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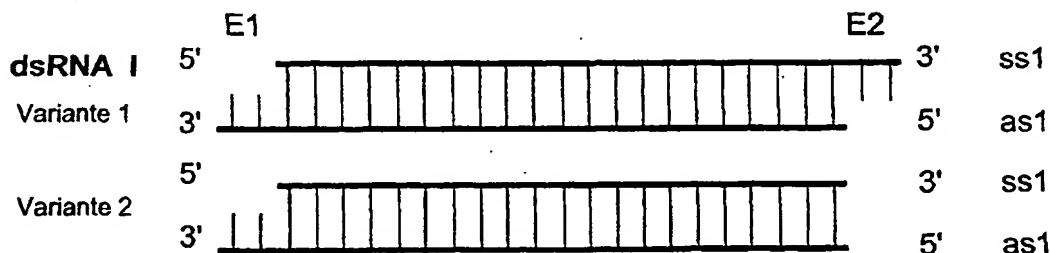
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(54) Titre : PROCEDE POUR INHIBER L'EXPRESSION D'UN GENE CIBLE
(54) Title: METHOD FOR INHIBITING THE EXPRESSION OF A TARGET GENE



(57) Abrégé/Abstract:

The invention relates to a method for inhibiting the expression of a target gene in a cell, comprising the following steps: introduction of an amount of at least one dual-stranded ribonucleic acid (dsRNA I) which is sufficient to inhibit the expression of the target gene. The dsRNA I has a dual-stranded structure formed by a maximum of 49 successive nucleotide pairs. One strand (as1) or at least one section of the one strand (as1) of the dual-stranded structure is complementary to the sense strand of the target gene. The dsRNA has an overhang on the end (E1) of dsRNA I formed by 1 - 4 nucleotides.

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Patent Claims

1. Method for inhibiting the expression of a target gene in a cell, comprising the following steps:

Introduction of at least one double-stranded ribonucleic acid (dsRNA I) in a quantity sufficient to inhibit expression of the target gene,

whereby dsRNA I exhibits a double-stranded structure consisting of a maximum of 49 successive nucleotide pairs, and whereby one strand (as1) or at least one segment of the strand (as1) of the double-stranded structure is complementary to the target gene,

and whereby at least one end (E1, E2) of dsRNA I exhibits an overhang consisting of 1 to 4 nucleotides.

2. Method in accordance with Claim 1, whereby dsRNA I exhibits the overhang at the 3'-end of one strand (as1) and/or at the 3'-end of the other strand (ss1).

3. Method in accordance with Claim 1 or 2, whereby dsRNA I has a smooth configuration at one end (E1, E2).

4. Method in accordance with Claim 3, whereby the smooth end (E1, E2) contains the 5'-end of one strand (as1).

5. Method in accordance with one of the preceding claims, whereby the overhang consists of 1 to 4 nucleotides, preferably of 1 or 2 nucleotides.

6. Method in accordance with one of the preceding claims, whereby at least one further double-stranded ribonucleic

acid (dsRNA II) having a configuration according to the dsRNA I as defined in the preceding claims, is introduced into the cell, whereby one strand (as1) of dsRNA I is complementary to a first region (B1) of the target gene, and
5 whereby another strand (as2) or at least one segment of the other strand (as2) of dsRNA II is complementary to a second region (B2) of the target gene.

7. Method in accordance with one of the preceding claims,
10 whereby dsRNA I and/or dsRNA II exhibits a length of fewer than 25 successive nucleotide pairs, preferably 19 to 23.

8. Method in accordance with one of the preceding claims,
15 whereby the first (B1) and the second (B2) region overlap segmentally or adjoin each other.

9. Method in accordance with one of the preceding claims,
whereby the first (B1) and the second (B2) region are separated from each other.

20 10. Method in accordance with one of the preceding claims, whereby the target gene exhibits one of the sequences SQ001 to SQ140.

25 11. Method in accordance with one of the preceding claims, whereby the target gene is selected from the following group: oncogene, cytokine gene, Id protein gene, prion gene, genes from angiogenesis-inducing molecules, from adhesion molecules, and from cell-surface receptors; genes
30 from proteins that are involved in metastatic and/or invasive

processes; genes from proteinases as well as molecules that regulate apoptosis and the cell cycle.

12. Method in accordance with one of the preceding claims,
whereby the target gene is the MDR1 gene.

5 13. Method in accordance with one of the preceding claims,
whereby one of the sequences SQ141-173 or a dsRNA construct
being combined of two antisense- (as1/2) and sense sequences
(ss1/2) belonging together and belonging to sequences SQ141-
173 are used as the dsRNA I/II.

10

14. Method in accordance with one of the preceding claims,
whereby expression is inhibited according to the principle
of RNA interference.

15 15. Method in accordance with one of the preceding claims,
whereby the target gene is expressed in pathogenic
organisms, preferably in plasmodia.

16. Method in accordance with one of the preceding claims,
20 whereby the target gene is a component of a virus or viroid.

17. Method in accordance with Claim 16, whereby the virus is a
human pathogenic virus or viroid.

25 18. Method in accordance with Claim 16, whereby the virus or
viroid is a virus or viroid that is pathogenic in animals or
plants.

19. Method in accordance with one of the preceding claims,
30 whereby unpaired nucleotides are substituted by nucleoside
thiophosphates.

20. Method in accordance with one of the preceding claims,
whereby at least one end (E1, E2) of dsRNA I/II is modified

in order to counter decomposition in the cell or dissociation in the individual strands.

21. Method in accordance with one of the preceding claims,
5 whereby the cohesion of the double-stranded structure effected by the complementary nucleotide pairs is increased by at least one chemical bond.
22. Method in accordance with one of the preceding claims,
10 whereby the chemical link is achieved either by a covalent or ionic bond, a hydrogen bond, hydrophobic interaction, preferably by means of van der Waals or stacking interactions, or by means of metal-ion coordination.
23. Method in accordance with one of the preceding claims,
15 whereby the chemical link is formed in the vicinity of one end (E1, E2).
24. Method in accordance with one of the preceding claims,
20 whereby the chemical link is created by one or several linkage groups, whereby the linkage groups are preferably poly-(oxyphosphinico-oxy-1,3-propandiol) and/or oligoethyleneglycol chains.
25. Method in accordance with one of the preceding claims,
25 whereby the chemical link is formed by using branched nucleotide analogs instead of nucleotides.
26. Method in accordance with one of the preceding claims,
30 whereby the chemical link is formed by purine analogs.
27. Method in accordance with one of the preceding claims,
whereby the chemical link is formed by azabenzene units.

28. Method in accordance with one of the preceding claims,
whereby at least one of the following groups is used in
creating the chemical link: methylene blue; bifunctional
groups, preferably bis-(2-chlorethyl)-amine; N-acetyl-N'-(p-
glyoxyl-benzoyl)-cystamine; 4-thiouracil; psoralen.

29. Method in accordance with one of the preceding claims,
whereby the chemical link is formed by thiophosphoryl groups
that are attached in the vicinity of the ends (E1, E2) of
the double-stranded region.

30. Method in accordance with one of the preceding claims,
whereby the chemical link is formed by triple helix bonds
that are present in the vicinity of the ends (E1, E2).

31. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is enclosed in micellar structures,
most advantageously in liposomes.

32. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is bound to, associated with, or
enclosed by at least one viral case protein that stems from
a virus, is derived from it, or is synthetically produced.

33. Method in accordance with one of the preceding claims,
whereby the coat protein is derived from polyomavirus.

34. Method in accordance with one of the preceding claims,
whereby the coat protein contains Virus Protein 1 (VP1)
and/or Virus Protein 2 (VP2) of the polyomavirus.

35. Method in accordance with one of the preceding claims,
whereby at the formation of a capsid or capsid-like

structure, the one side is turned toward the inside of the capsid or capsid-like structure.

36. Method in accordance with one of the preceding claims,
5 whereby the one strand (as1, as2) of dsRNA I/II is complementary to the primary or processed RNA transcript of the target gene.

37. Method in accordance with one of the preceding claims,
10 whereby the cell is a vertebrate cell or a human cell.

38. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is administered to a mammal at a maximum dosage of 5 mg/kg body weight per day, preferably to
15 a human.

39. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is mixed in a buffer solution for application.
20

40. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is administered orally or by intravenous, intratumoral, or intraperitoneal injection or infusion, or by inhalation.
25

41. Use of a double-stranded ribonucleic acid (dsRNA I) for inhibiting the expression of the target gene in a cell, whereby dsRNA I exhibits a double-stranded structure consisting of a maximum of 49 successive nucleotide pairs,
30 and whereby one strand (as1) or at least one segment of a strand (as1) of the double-stranded structure is complementary to the target gene,

and whereby dsRNA I exhibits an overhang consisting of 1 to 4 nucleotides at at least one end (E1, E2).

5 42. Use in accordance with Claim 41, whereby dsRNA I exhibits the overhang at the 3'-end of one strand (as1) and/or at the 3'-end of the other strand (ss1).

43. Use in accordance with Claim 41 or 42, whereby dsRNA I has a smooth configuration at one end (E1, E2).

10

44. Use in accordance with Claim 43, whereby the smooth end (E1, E2) contains the 5'-end of one strand (as1).

15 45. Use in accordance with one of the Claims 41 to 44, whereby the overhang consists of 1 to 4 nucleotides, preferably of 1 or 2 nucleotides.

20 46. Use in accordance with Claims 41 to 45, whereby at least one further double-stranded ribonucleic acid (dsRNA II) having a configuration according to dsRNA I as defined in claims 41 to 45, is introduced into the cell, whereby the one strand (as1) or at least one segment of the strand (as1) of the double-stranded structure of the dsRNA I is complementary to a first region (B1) of the sense strand of the target gene,
25 and whereby the other strand (as2) or at least one segment of the other strand (as2) of the double-stranded structure of dsRNA II is complementary to a second region (B2) of the target gene.

30 47. Use in accordance with one of the Claims 41 to 46, whereby the dsRNA I and/or dsRNA II exhibits a length of fewer than 25, preferably 19 to 23, successive nucleotide pairs.

48. Use in accordance with one of the Claims 41 to 47, whereby the first (B1) and second region (B2) overlap segmentally or adjoin each other.
- 5 49. Use in accordance with one of the Claims 41 to 48, whereby the first (B1) and second region (B2) are separated from each other.
- 10 50. Use in accordance with one of the Claims 41 to 49, whereby the target gene exhibits one of the sequences SQ001 to SQ140.
- 15 51. Use in accordance with one of the Claims 41 to 50, whereby the target gene is selected from the following group:
oncogene, cytokine gene, Id protein gene, prion gene, genes from angiogenesis-inducing molecules, from adhesion molecules, and from cell-surface receptors; genes from proteins that are involved in metastatic and/or invasive processes; genes from proteinases as well as molecules that regulate apoptosis and the cell cycle.
- 20 52. Use in accordance with one of the Claims 41 to 51, whereby the target gene is the MRD1 gene.
- 25 53. Use in accordance with one of the Claims 41 to 52, whereby one of the sequences SQ141-173 or a dsRNA construct being combined of two antisense- (as1/2) and sense sequences (ss1/2) belonging together and belonging to sequences SQ141-173 are used as the dsRNA I/II.
- 30 54. Use in accordance with one of the Claims 41 to 53, whereby expression is inhibited according to the principal of RNA interference.

55. Use in accordance with one of the Claims 41 to 54, whereby the target gene is expressed in pathogenic organisms, preferably in plasmodia.
- 5 56. Use in accordance with one of the Claims 41 to 55, whereby the target gene is a component of a virus or viroid.
57. Use in accordance with Claim the 56, whereby the virus is a human pathogenic virus or viroid.
- 10 58. Use in accordance with claim 56, whereby the virus or viroid is a virus or viroid that is pathogenic in animals or plants.
- 15 59. Use in accordance with one of the Claims 41 to 58, whereby unpaired nucleotides are substituted by nucleoside thiophosphates.
- 20 60. Use in accordance with one of the Claims 41 to 59, whereby at least one end (E1, E2) of the dsRNA is modified in order to counter decomposition in the cell or dissociation in the individual strands.
- 25 61. Use in accordance with one of the Claims 41 to 60, whereby the cohesion of the double-stranded structure effected by the complementary nucleotide pairs is increased by at least one chemical bond.
- 30 62. Use in accordance with one of the Claims 41 to 61, whereby the chemical link is achieved either by a covalent or ionic bond, a hydrogen bond, hydrophobic interaction, preferably by means of van der Waals or stacking interactions, or by means of metal-ion coordination.

63. Use in accordance with one of the Claims 41 to 62, whereby the chemical link is formed in the vicinity of one end (E1, E2).

5 64. Use in accordance with one of the Claims 41 to 63, whereby the chemical link is created by one or several linkage groups, whereby the linkage groups are preferably poly-(oxyphosphinico-oxy-1,3-propandiol) and/or oligoethyleneglycol chains.

10 65. Use in accordance with one of the Claims 41 to 64, whereby the chemical link is formed by using branched nucleotide analogs instead of nucleotides.

15 66. Use in accordance with one of the Claims 41 to 65, whereby the chemical link is formed by purine analogs.

67. Use in accordance with one of the Claims 41 to 66, whereby the chemical link is formed by azabenzene units.

20 68. Use in accordance with one of the Claims 41 to 67, whereby at least one of the following groups is used in creating the chemical link: methylene blue; bifunctional groups, preferably bis-(2-chlorethyl)-amine; N-acetyl-N'-(p-glyoxyl-
25 benzoyl)-cystamine; 4-thiouracil; psoralen.

69. Use in accordance with one of the Claims 41 to 68, whereby the chemical link is formed by thiophosphoryl groups that are attached in the vicinity of the ends (E1, E2) of the
30 double-stranded region.

70. Use in accordance with one of the Claims 41 to 69, whereby the link is produced by triple helix bonds present in the vicinity of the ends (E1, E2).

71. Use in accordance with one of the Claims 41 to 70, whereby the dsRNA I/II is enclosed in micellar structures, most advantageously in liposomes.

5

72. Use in accordance with one of the Claims 41 to 71, whereby the dsRNA I/II is bound to, associated with, or enclosed by at least one viral case protein that stems from a virus, is derived from it, or is synthetically produced.

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73. Use in accordance with one of the Claims 41 to 72, whereby the case protein is derived from polyomavirus.

74. Use in accordance with one of the Claims 41 to 73, whereby the case protein contains Virus Protein 1 (VP1) and/or Virus Protein 2 (VP2) of the polyomavirus.

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75. Use in accordance with one of the Claims 41 to 74, whereby at the formation of a capsid or capsid-like structure, the one side is turned toward the inside of the capsid or capsid-like structure.

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76. Use in accordance with one of the Claims 41 to 75, whereby the one strand (as1, as2) of dsRNA I/II is complementary to the primary or processed RNA transcript of the target gene.

25

77. Use in accordance with one of the Claims 41 to 76, whereby the cell is a vertebrate cell or a human cell.

78. Use in accordance with one of the Claims 41 to 77, whereby the dsRNA I/II is administered to a mammal at a maximum dosage of 5 mg/kg body weight per day, preferably to human being.

30

79. Use in accordance with one of the Claims 41 to 78, whereby the dsRNA I/II is mixed with a buffer solution for application.

5 80. Use in accordance with one of the Claims 41 to 79, whereby the dsRNA I/II is administered orally or by intravenous, intratumoral, or intraperitoneal injection or infusion, or by inhalation.

10 81. Medicament for inhibiting the expression of a target gene in a cell, containing a double-stranded ribonucleic acid (dsRNA I) in a dosage sufficient to inhibit the expression of the target gene,

15 whereby dsRNA I exhibits a double-stranded structure consisting of a maximum of 49 successive nucleotide pairs,

and whereby one strand (as1) or at least one segment of the strand (as1) of the double-stranded structure is
20 complementary to the target gene,

and whereby at least one end (E1, E2) of the dsRNA I exhibits an overhang consisting of 1 to 4 nucleotides.

25 82. Medicament in accordance with Claim 81, whereby dsRNA I exhibits the overhang at the 3'-end of one strand (as1) and/or at the 3'-end of the other strand (ss1).

83. Medicament in accordance with Claim 81 or 82, whereby the
30 dsRNA I has a smooth configuration at one end (E1, E2).

84. Medicament in accordance with Claim 83, whereby the smooth end (E1, E2) contains the 5'-end of the first strand (as1).

85. Medicament in accordance with Claims 81 to 84, whereby the overhang consists of 1 to 4 nucleotides, preferably of 1 or 2 nucleotides.

5 86. Medicament in accordance with one of the Claims 81 to 85, whereby at least one further double-stranded ribonucleic acid (dsRNA II) having a configuration according to the dsRNA I as defined in Claims 81 to 85, and whereby the one strand (as1) of dsRNA I is complementary to a first region
10 (B1) of the target gene, and whereby another strand (as2) or at least one segment of the other strand (as2) of dsRNA II is complementary to a second region (B2) of the target gene.

87. Medicament in accordance with one of the Claims 81 to 86,
15 whereby the dsRNA I and/or dsRNA II exhibits a length of fewer than 25, preferably in 19 to 23, successive nucleotide pairs.

88. Medicament in accordance with one of the Claims 81 to 87,
20 whereby the first (B1) and the second region (B2) overlap segmentally or adjoin each other.

89. Medicament in accordance with one of the Claims 81 to 88,
25 whereby the target gene exhibits one of the sequences SQ001 to SQ140.

90. Medicament in accordance with one of the Claims 81 to 89,
whereby the target gene is selected from the following group: oncogene, cytokine gene, Id protein gene, prion gene,
30 genes from angiogenesis-inducing molecules, from adhesion molecules, and from cell-surface receptors; genes from proteins that are involved in metastatic and/or invasive processes; genes from proteinases as well as molecules that regulate apoptosis and the cell cycle.

91. Medicament in accordance with one of the Claims 81 to 90,
whereby the target gene is the MRD1 gene.

5 92. Medicament in accordance with one of the Claims 81 to 91,
whereby one of the sequences SQ141-173 or a dsRNA construct
being combined of two antisense- (as1/2) and sense sequences
(ss1/2) belonging together and belonging to sequences SQ141-
173 are used as the dsRNA I/II.

10

93. Medicament in accordance with one of the Claims 81 to 92,
whereby expression is inhibited according to the principle
of RNA interference.

15 94. Medicament in accordance with one of the Claims 81 to 93,
whereby the target gene is expressed in pathogenic
organisms, most advantageously in plasmodia.

95. Medicament in accordance with one of the Claims 81 to 94,
20 whereby the target gene is a component of a virus or viroid.

96. Medicament in accordance with Claim 95, whereby the virus is
a human pathogenic virus or viroid.

25 97. Medicament in accordance with Claim 95, whereby the virus or
viroid is a virus or viroid that is pathogenic in animals or
plants.

98. Medicament in accordance with one of the Claims 81 to 97,
30 whereby unpaired nucleotides are substituted with nucleoside
thiophosphates.

99. Medicament in accordance with one of the Claims 81 to 98,
whereby at least one end (E1, E2) of dsRNA I/II is modified

in order to counter decomposition in the cell or dissociation in the individual strand.

100. Medicament in accordance with one of the Claims 81 to 99,
5 / whereby the cohesion of the double-stranded structure effected by the complementary nucleotide pairs is increased by at least one chemical bond.
101. Medicament in accordance with one of the Claims 81 to 100,
10 whereby the chemical link is achieved either by a covalent or ionic bond, a hydrogen bond, hydrophobic interaction, preferably by means of van der Waals or stacking interactions, or by means of metal-ion coordination.
- 15 102. Medicament in accordance with one of the Claims 81 to 101, whereby the chemical link is formed in the vicinity of one end (E1, E2).
103. Medicament in accordance with one of the Claims 81 to 102,
20 whereby the chemical link is created by one or several linkage groups, whereby the linkage groups are preferably poly-(oxyphosphinico-oxy-1,3-propandiol) and/or oligoethyleneglycol chains.
- 25 104. Medicament in accordance with one of the Claims 81 to 103, whereby the chemical link is formed by using branched nucleotide analogs instead of nucleotides.
105. Medicament in accordance with one of the Claims 81 to 104,
30 whereby the chemical link is formed by purine analogs.
106. Medicament in accordance with one of the Claims 81 to 105, whereby the chemical link is formed by azabenzene units.

107. Medicament in accordance with one of the Claims 81 to 106,
whereby at least one of the following groups is used in
creating the chemical link: methylene blue; bifunctional
groups, preferably bis-(2-chlorethyl)-amine; N-acetyl-N'-(p-
glyoxyl-benzoyl)-cystamine; 4-thiouracil; psoralen.
108. Medicament in accordance with one of the Claims 81 to 107,
whereby the chemical link is formed by thiophosphoryl groups
that are attached in the vicinity of the ends (E1, E2) of
the double-stranded region.
109. Medicament in accordance with one of the Claims 81 to 108,
whereby the chemical link is formed by triple helix bonds
that are present in the vicinity of the ends (E1, E2).
110. Medicament in accordance with one of the Claims 81 to 109,
whereby the dsRNA I/II is enclosed in micellar structures,
most advantageously in liposomes.
111. Medicament in accordance with one of the Claims 81 to 110,
whereby the dsRNA I/II is bound to, associated with, or
enclosed by at least one viral case protein that stems from
a virus, is derived from it, or is synthetically produced.
112. Medicament in accordance with one of the Claims 81 to 111,
whereby the coat protein is derived from polyomavirus.
113. Medicament in accordance with one of the Claims 81 to 112,
whereby the coat protein contains Virus Protein 1 (VP1)
and/or Virus Protein 2 (VP2) of the polyomavirus.
114. Medicament in accordance with one of the Claims 81 to 113,
whereby at the formation of a capsid or capsid-like

structure, the one side is turned toward the inside of the capsid or capsid-like structure.

115. Medicament in accordance with one of the Claims 81 to 114,
5 whereby the one strand (as1, as2) of dsRNA I/II is complementary to the primary or processed RNA transcript of the target gene.

116. Medicament in accordance with one of the Claims 81 to 115,
10 whereby the cell is a vertebrate cell or a human cell.

117. Medicament in accordance with one of the Claims 81 to 116,
whereby the first (B1) and the second region (B2) are separated from each other.

15 118. Medicament in accordance with one of the Claims 81 to 117, whereby the dsRNA is administered at a maximum amount of 5 mg per dose.

20 119. Medicament in accordance with one of the Claims 81 to 118, whereby the dsRNA is mixed in a buffer solution for application.

25 120. Medicament in accordance with one of the Claims 81 to 119, whereby the dsRNA is administered orally or by intravenous, intratumoral, or intraperitoneal injection or infusion, or by inhalation.

30 121. Method for inhibiting the expression of a target gene in a cell, comprising the following steps:

Introduction of at least one double-stranded ribonucleic acid (dsRNA I) in a quantity sufficient to inhibit expression of the target gene,

whereby dsRNA I exhibits a double-stranded structure consisting of a maximum of 49 successive nucleotide pairs, and whereby one strand (as1) or at least one segment of the strand (as1) of the double-stranded structure is complementary to the target gene,

and whereby at least one end (E1, E2) of the dsRNA I exhibits an overhang consisting of 1 to 4 nucleotides.

122. Method in accordance with Claim 1, whereby dsRNA I exhibits the overhang at the 3'-end of one strand (as1) and/or at the 3'-end of the other strand (ss1).

123. Method in accordance with Claim 1 or 2, whereby the dsRNA I has a smooth configuration at one end (E1, E2).

124. Method in accordance with Claim 3, whereby the smooth end (E1, E2) contains the 5'-end of one strand (as1).

125. Method in accordance with one of the preceding claims, whereby the overhang consists of 1 to 4 nucleotides, preferably of 1 or 2 nucleotides.

126. Method in accordance with one of the preceding claims, whereby at least one further double-stranded ribonucleic acid (dsRNA II) having a configuration according to the dsRNA I as defined in the preceding claims, is introduced into the cell, whereby the one strand (as1) of dsRNA I is complementary to a first region (B1) of the target gene, and whereby another strand (as2) or at least one segment of the other strand (as2) of dsRNA II is complementary to a second region (B2) of the target gene.

127. Method in accordance with one of the preceding claims,
whereby the dsRNA I and/or dsRNA II exhibits a length of
fewer than 25 successive nucleotide pairs, preferably 19 to
23.

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128. Method in accordance with one of the preceding claims,
whereby the first (B1) and the second (B2) region overlap
segmentally or adjoin each other.

10 129. Method in accordance with one of the preceding claims,
whereby the first (B1) and the second (B2) region are
separated from each other.

130. Method in accordance with one of the preceding claims,
15 whereby the target gene exhibits one of the sequences SQ001
to SQ140.

131. Method in accordance with one of the preceding claims,
whereby the target gene is selected from the following
20 group: oncogene, cytokine gene, Id protein gene, prion
gene, genes from angiogenesis-inducing molecules, from
adhesion molecules, and from cell-surface receptors; genes
from proteins that are involved in metastatic and/or
invasive processes; genes from proteinases as well as
25 molecules that regulate apoptosis and the cell cycle.

132. Method in accordance with one of the preceding claims,
whereby the target gene is the MDR1 gene.

30 133. Method in accordance with one of the preceding claims,
whereby one of the sequences SQ141-173 or a dsRNA construct
being combined of two antisense- (as1/2) and sense sequences
(ss1/2) belonging together and belonging to sequences SQ141-
173 are used as the dsRNA I/II.

134. Method in accordance with one of the preceding claims,
whereby expression is inhibited according to the principle
of RNA interference.

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135. Method in accordance with one of the preceding claims,
whereby the target gene is expressed in pathogenic
organisms, preferably in plasmodia.

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136. Method in accordance with one of the preceding claims,
whereby the target gene is a component of a virus or viroid.

137. Method in accordance with Claim 16, whereby the virus is a
human pathogenic virus or viroid.

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138. Method in accordance with Claim 16, whereby the virus or
viroid is a virus or viroid that is pathogenic in animals or
plants.

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139. Method in accordance with one of the preceding claims,
whereby unpaired nucleotides are substituted by nucleoside
thiophosphates.

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140. Method in accordance with one of the preceding claims,
whereby at least one end (E1, E2) of dsRNA I/II is modified
in order to counter decomposition in the cell or
dissociation in the individual strand.

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141. Method in accordance with one of the preceding claims,
whereby the cohesion of the double-stranded structure
effected by the complementary nucleotide pairs is increased
by at least one chemical bond.

142. Method in accordance with one of the preceding claims,
whereby the chemical link is achieved either by a covalent
or ionic bond, a hydrogen bond, hydrophobic interaction,
preferably by means of van der Waals or stacking
5 interactions, or by means of metal-ion coordination.

143. Method in accordance with one of the preceding claims,
whereby the chemical link is formed in the vicinity of one
end (E1, E2).

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144. Method in accordance with one of the preceding claims,
whereby the chemical link is created by one or several
linkage groups, whereby the linkage groups are preferably
poly-(oxyphosphinico-oxy-1,3-propandiol) and/or
15 oligoethyleneglycol chains.

145. Method in accordance with one of the preceding claims,
whereby the chemical link is formed by using branched
nucleotide analogs instead of nucleotides.

20

146. Method in accordance with one of the preceding claims,
whereby the chemical link is formed by purine analogs.

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147. Method in accordance with one of the preceding claims,
whereby the chemical link is formed by azabenzene units.

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148. Method in accordance with one of the preceding claims,
whereby at least one of the following groups is used in
creating the chemical link: methylene blue; bifunctional
groups, preferably bis-(2-chlorethyl)-amine; N-acetyl-N'-(p-
glyoxyl-benzoyl)-cystamine; 4-thiouracil; psoralen.

149. Method in accordance with one of the preceding claims,
whereby the chemical link is formed by thiophosphoryl groups

that are attached in the vicinity of the ends (E1, E2) of the double-stranded region.

150. Method in accordance with one of the preceding claims,
5 whereby the chemical link is formed by triple helix bonds that are present in the vicinity of the ends (E1, E2).

151. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is enclosed in micellar structures,
10 most advantageously in liposomes.

152. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is bound to, associated with, or
enclosed by at least one viral case protein that stems from
15 a virus, is derived from it, or is synthetically produced.

153. Method in accordance with one of the preceding claims,
whereby the coat protein is derived from polyomavirus.

20 154. Method in accordance with one of the preceding claims,
whereby the coat protein contains Virus Protein 1 (VP1)
and/or Virus Protein 2 (VP2) of the polyomavirus.

155. Method in accordance with one of the preceding claims,
25 whereby at the formation of a capsid or capsid-like
structure, the one side is turned toward the inside of the
capsid or capsid-like structure.

156. Method in accordance with one of the preceding claims,
30 whereby the one strand (as1, as2) of dsRNA I/II is
complementary to the primary or processed RNA transcript of
the target gene.

157. Method in accordance with one of the preceding claims,
whereby the cell is a vertebrate cell or a human cell.

158. Method in accordance with one of the preceding claims,
5 whereby the dsRNA I/II is administered to a mammal at a
maximum dosage of 5 mg/kg body weight per day, preferably to
human being.

159. Method in accordance with one of the preceding claims,
10 whereby the dsRNA I/II is mixed in a buffer solution for
application.

160. Method in accordance with one of the preceding claims,
whereby the dsRNA I/II is administered orally or by
15 intravenous, intratumoral, or intraperitoneal injection or
infusion, or by inhalation.

161. Use of a double-stranded ribonucleic acid (dsRNA I) for
inhibiting the expression of the target gene in a cell,
20 whereby dsRNA I exhibits a double-stranded structure
consisting of a maximum of 49 successive nucleotide pairs,
and whereby one strand (as1) or at least one segment of a
strand (as1) of the double-stranded structure is
complementary to the target gene, and whereby dsRNA I
25 exhibits an overhang consisting of 1 to 4 nucleotides at at
least one end (E1, E2).

162. Use in accordance with Claim 41, whereby dsRNA I exhibits
the overhang at the 3'-end of one strand (as1) and/or at the
30 3'-end of the other strand (ss1).

163. Use in accordance with Claim 41 or 42, whereby the dsRNA I
has a smooth configuration at one end (E1, E2).

164. Use in accordance with Claim 43, whereby the smooth end(E1, E2) contains the 5'-end of one strand (as1).

165. Use in accordance with one of the Claims 41 to 44, whereby
5 the overhang consists of 1 to 4 nucleotides, preferably of 1 or 2 nucleotides.

166. Use in accordance with Claims 41 to 45, whereby at least one
10 further double-stranded ribonucleic acid (dsRNA II), having a configuration according to the dsRNA I as defined in the preceding claims 41 to 45, is introduced into the cell, whereby the one strand (as1) or at least one segment of the strand (as1) of the double-stranded structure of the dsRNA I is complementary to a first region (B1) of the sense strand
15 of the target gene, and whereby the other strand (as2) or at least one segment of the other strand (as2) of the double-stranded structure of dsRNA II is complementary to a second region (B2) of the target gene.

20 167. Use in accordance with one of the Claims 41 to 47, whereby the dsRNA I and/or dsRNA II exhibits a length of fewer than 25, preferably 19 to 23, successive nucleotide pairs.

168. Use in accordance with one of the Claims 41 to 47, whereby
25 the first (B1) and second region (B2) overlap segmentally or adjoin each other.

169. Use in accordance with one of the Claims 41 to 48, whereby
30 the first (B1) and second region (B2) are separated from each other.

170. Use in accordance with one of the Claims 41 to 49, whereby
the target gene exhibits one of the sequences SQ001 to
SQ140.

171. Use in accordance with one of the Claims 41 to 50, whereby the target gene is selected from the following group: oncogene, cytokine gene, Id protein gene, prion gene, genes from angiogenesis-inducing molecules, from adhesion molecules, and from cell-surface receptors; genes from proteins that are involved in metastatic and/or invasive processes; genes from proteinases as well as molecules that regulate apoptosis and the cell cycle.

172. Use in accordance with one of the Claims 41 to 51, whereby the target gene is the MRD1 gene.

173. Use in accordance with one of the Claims 41 to 52, whereby one of the sequences SQ141-173 or a dsRNA construct being combined of two antisense- (as1/2) and sense sequences (ss1/2) belonging together and belonging to sequences SQ141-173 are used as the dsRNA I/II.

174. Use in accordance with one of the Claims 41 to 53, whereby expression is inhibited according to the principal of RNA interference.

175. Use in accordance with one of the Claims 41 to 54, whereby the target gene is expressed in pathogenic organisms, preferably in plasmodia.

176. Use in accordance with one of the Claims 41 to 55, whereby the target gene is a component of a virus or viroid.

177. Use in accordance with Claim 56, whereby the virus is a human pathogenic virus or viroid.

178. Use in accordance with Claim 56 whereby the virus or viroid is a virus or viroid that is pathogenic in animals or plants.
- 5 179. Use in accordance with one of the Claims 41 to 58, whereby unpaired nucleotides are substituted by nucleoside thiophosphates.
- 10 180. Use in accordance with one of the Claims 41 to 59, whereby at least one end (E1, E2) of the dsRNA is modified in order to counter decomposition in the cell or dissociation in the individual strand.
- 15 181. Use in accordance with one of the Claims 41 to 60, whereby the cohesion of the double-stranded structure effected by the complementary nucleotide pairs is increased by at least one chemical bond.
- 20 182. Use in accordance with one of the Claims 41 to 61, whereby the chemical link is achieved either by a covalent or ionic bond, a hydrogen bond, hydrophobic interaction, preferably by means of van der Waals or stacking interactions, or by means of metal-ion coordination.
- 25 183. Use in accordance with one of the Claims 41 to 62, whereby the chemical link is formed in the vicinity of one end (E1, E2).
- 30 184. Use in accordance with one of the Claims 41 to 63, whereby the chemical link is created by one or several linkage groups, whereby the linkage groups are preferably poly-(oxyphosphinico-oxy-1,3-propandiol) and/or oligoethyleneglycol chains.

185. Use in accordance with one of the Claims 41 to 64, whereby the chemical link is formed by using branched nucleotide analogs instead of nucleotides.

5 186. Use in accordance with one of the Claims 41 to 65, whereby the chemical link is formed by purine analogs.

187. Use in accordance with one of the Claims 41 to 66, whereby the chemical link is formed by azabenzene units.

10

188. Use in accordance with one of the Claims 41 to 67, whereby at least one of the following groups is used in creating the chemical link: methylene blue; bifunctional groups, preferably bis-(2-chlorethyl)-amine; N-acetyl-N'-(p-glyoxyl-
15 benzoyl)-cystamine; 4-thiouracil; psoralen.

20

189. Use in accordance with one of the Claims 41 to 68, whereby the chemical link is formed by thiophosphoryl groups that are attached in the vicinity of the ends (E1, E2) of the double-stranded region.

25

190. Use in accordance with one of the Claims 41 to 69, whereby the link is produced by triple helix bonds present in the vicinity of the ends (E1, E2).

191. Use in accordance with one of the Claims 41 to 70, whereby the dsRNA I/II is enclosed in micellar structures, most advantageously in liposomes.

30

192. Use in accordance with one of the Claims 41 to 71, whereby the dsRNA I/II is bound to, associated with, or enclosed by at least one viral case protein that stems from a virus, is derived from it, or is synthetically produced.

193. Use in accordance with one of the Claims 41 to 72, whereby the case protein is derived from polyomavirus.
194. Use in accordance with one of the Claims 41 to 73, whereby
5 the case protein contains Virus Protein 1 (VP1) and/or Virus Protein 2 (VP2) of the polyomavirus.
195. Use in accordance with one of the Claims 41 to 74, whereby
10 at the formation of a capsid or capsid-like structure, the one side is turned toward the inside of the capsid or capsid-like structure.
196. Use in accordance with one of the Claims 41 to 75, whereby
15 the one strand (as1, as2) of dsRNA I/II is complementary to the primary or processed RNA transcript of the target gene.
197. Use in accordance with one of the Claims 41 to 76, whereby the cell is a vertebrate cell or a human cell.
- 20 198. Use in accordance with one of the Claims 41 to 77, whereby the dsRNA I/II is administered to a mammal at a maximum dosage of 5 mg/kg body weight per day, preferably to human being.
- 25 199. Use in accordance with one of the Claims 41 to 78, whereby the dsRNA I/II is mixed with a buffer solution for application.
- 30 200. Use in accordance with one of the Claims 41 to 79, whereby the dsRNA I/II is administered orally or by intravenous, intratumoral, or intraperitoneal injection or infusion, or by inhalation.

201. Medicament for inhibiting the expression of a target gene in a cell containing a double-stranded ribonucleic acid (dsRNA I) in a dosage sufficient to inhibit the expression of the target gene.

5

whereby dsRNA I exhibits a double-stranded structure consisting of a maximum of 49 successive nucleotide pairs,

10

and whereby one strand (as1) or at least one segment of the strand (as1) of the double-stranded structure is complementary to the target gene,

15

and whereby at least one end (E1, E2) of the dsRNA I exhibits an overhang consisting of 1 to 4 nucleotides.

202. Medicament in accordance with Claim 81, whereby dsRNA I exhibits the overhang at the 3'-end of one strand (as1) and/or at the 3'-end of the other strand (ss1).

203. Medicament in accordance with Claim 81 or 82, whereby the dsRNA I has a smooth configuration at one end (E1, E2).

204. Medicament in accordance with Claim 83, whereby the smooth end (E1, E2) contains the 5'-end of the first strand (as1).

25

205. Medicament in accordance with Claims 81 to 84, whereby the overhang consists of 1 to 4 nucleotides, preferably of 1 or 2 nucleotides.

206. Medicament in accordance with one of the Claims 81 to 85, whereby at least one further double-stranded ribonucleic acid (dsRNA II) having a configuration according to the dsRNA I as defined in Claims 81 to 85, and whereby the one strand (as1) of dsRNA I is complementary to a first region

(B1) of the target gene, and whereby another strand (as2) or at least one segment of the other strand (as2) of dsRNA II is complementary to a second region (B2) of the target gene.

5 207. Medicament in accordance with one of the Claims 81 to 86, whereby the dsRNA I and/or dsRNA II exhibits a length of fewer than 25, preferably in 19 to 23, successive nucleotide pairs.

10 208. Medicament in accordance with one of the Claims 81 to 87, whereby the first (B1) and the second region (B2) overlap segmentally or adjoin each other.

15 209. Medicament in accordance with one of the Claims 81 to 88, whereby the target gene exhibits one of the sequences SQ001 to SQ140.

20 210. Medicament in accordance with one of the Claims 81 to 89, whereby the target gene is selected from the following group: oncogene, cytokine gene, Id protein gene, prion gene, genes from angiogenesis-inducing molecules, from adhesion molecules, and from cell-surface receptors; genes from proteins that are involved in metastatic and/or invasive processes; genes from proteinases as well as molecules that
25 regulate apoptosis and the cell cycle.

211. Medicament in accordance with one of the Claims 81 to 90, whereby the target gene is the MRD1 gene.

30 212. Medicament in accordance with one of the Claims 81 to 91, whereby one of the sequences SQ141-173 or a dsRNA construct being combined of two antisense- (as1/2) and sense sequences (ss1/2) belonging together and belonging to sequences SQ141-173 are used as the dsRNA I/II.

213. Medicament in accordance with one of the Claims 81 to 92,
whereby expression is inhibited according to the principle
of RNA interference.

5

214. Medicament in accordance with one of the Claims 81 to 93,
whereby the target gene is expressed in pathogenic
organisms, most advantageously in plasmodia.

10 215. Medicament in accordance with one of the Claims 81 to 94,
whereby the target gene is a component of a virus or viroid.

216. Medicament in accordance with Claim 95, whereby the virus is
a human pathogenic virus or viroid.

15

217. Medicament in accordance with Claim 95, whereby the virus or
viroid is a virus or viroid that is pathogenic in animals or
plants.

20 218. Medicament in accordance with one of the Claims 81 to 97,
whereby unpaired nucleotides are substituted with nucleoside
thiophosphates.

219. Medicament in accordance with one of the Claims 81 to 98,
25 whereby at least one end (E1, E2) of dsRNA I/II is modified
in order to counter decomposition in the cell or
dissociation in the individual strand.

220. Medicament in accordance with one of the Claims 81 to 99,
30 whereby the cohesion of the double-stranded structure
effected by the complementary nucleotide pairs is increased
by at least one chemical bond.

221. Medicament in accordance with one of the Claims 81 to 100,
whereby the chemical link is achieved either by a covalent
or ionic bond, a hydrogen bond, hydrophobic interaction,
preferably by means of van der Waals or stacking
5 interactions, or by means of metal-ion coordination.

222. 102. Medicament in accordance with one of the Claims 81 to
101, whereby the chemical link is formed in the vicinity of
one end (E1, E2).

10 223. Medicament in accordance with one of the Claims 81 to 102,
whereby the chemical link is created by one or several
linkage groups, whereby the linkage groups are preferably
poly-(oxyphosphinico-oxy-1,3-propandiol) and/or
15 oligoethyleneglycol chains.

224. Medicament in accordance with one of the Claims 81 to 103,
whereby the chemical link is formed by using branched
nucleotide analogs instead of nucleotides.

20 225. Medicament in accordance with one of the Claims 81 to 104,
whereby the chemical link is formed by purine analogs.

226. Medicament in accordance with one of the Claims 81 to 105,
25 whereby the chemical link is formed by azabenzene units.

227. Medicament in accordance with one of the Claims 81 to 106,
whereby at least one of the following groups is used in
creating the chemical link: methylene blue; bifunctional
30 groups, preferably bis-(2-chlorethyl)-amine; N-acetyl-N'-(p-
glyoxyl-benzoyl)-cystamine; 4-thiouracil; psoralen.

228. Medicament in accordance with one of the Claims 81 to 107,
whereby the chemical link is formed by thiophosphoryl groups

that are attached in the vicinity of the ends (E1, E2) of the double-stranded region.

229. Medicament in accordance with one of the Claims 81 to 108,
5 whereby the chemical link is formed by triple helix bonds that are present in the vicinity of the ends (E1, E2).

230. Medicament in accordance with one of the Claims 81 to 109,
10 whereby the dsRNA I/II is enclosed in micellar structures, most advantageously in liposomes.

231. Medicament in accordance with one of the Claims 81 to 110,
whereby the dsRNA I/II is bound to, associated with, or enclosed by at least one viral case protein that stems from
15 a virus, is derived from it, or is synthetically produced.

232. Medicament in accordance with one of the Claims 81 to 111,
whereby the coat protein is derived from polyomavirus.

20 233. Medicament in accordance with one of the Claims 81 to 112, whereby the coat protein contains Virus Protein 1 (VP1) and/or Virus Protein 2 (VP2) of the polyomavirus.

234. Medicament in accordance with one of the Claims 81 to 113,
25 whereby at the formation of a capsid or capsid-like structure, the one side is turned toward the inside of the capsid or capsid-like structure.

235. Medicament in accordance with one of the Claims 81 to 114,
30 whereby the one strand (as1, as2) of dsRNA I/II is complementary to the primary or processed RNA transcript of the target gene.

236. Medicament in accordance with one of the Claims 81 to 115,
whereby the cell is a vertebrate cell or a human cell.

237. Medicament in accordance with one of the Claims 81 to 116,
5 whereby the first (B1) and the second region (B2) are
separated from each other.

238. Medicament in accordance with one of the Claims 81 to 117,
whereby the dsRNA is administered at a maximum amount of 5
10 mg per dose.

239. Medicament in accordance with one of the Claims 81 to 118,
whereby the dsRNA is mixed in a buffer solution for
application.

15 240. Medicament in accordance with one of the Claims 81 to 119,
whereby the dsRNA is administered orally or by intravenous,
intratumoral, or intraperitoneal injection or infusion, or
by inhalation.

Method for inhibiting the Expression of a Target Gene

The invention concerns a method, a use, and a medicament for inhibiting expression of a target gene.

5

Methods to inhibit the expression of medically or biotechnologically interesting genes using a double-stranded ribonucleic acid (dsRNA) are known from WO 99/32619 and WO 00/44895. Although the known methods are highly effective, there
10 is nonetheless a need to further enhance their efficiency.

The object of the present invention is to remove the shortcomings in accordance with the state-of-the-art. In particular, a method, a use, and a medicament are to be
15 disclosed, by which even more efficient inhibition of the expression of a target gene is achievable.

This object is solved by the features of Claims 1, 41, and 81. Advantageous embodiments result from features of Claims 2 to 40,
20 42 to 80, and 82 to 120.

Surprisingly, with the features claimed in this invention, a drastic enhancement is achieved in the effectiveness of inhibition of the expression of a target gene in vitro and in
25 vivo. As a result of the particular formation of the dsRNA ends, both their efficiency in mediating the inhibitory action on the expression of a target gene as well as their stability can be affected in a targeted way. Active concentration in the cells is enhanced as a result of this enhanced stability.

30

In terms of the invention, "target gene" is understood to mean the DNA strand of a double-stranded DNA in the cell, which is complementary to a DNA strand, including all transcribed regions, that serves as a matrix for transcription. In other

words, the "target gene" is generally the sense strand. One strand, or antisense strand (as1) can be complementary to an RNA transcript or its processing products, e.g., an mRNA, formed during expression of a target gene. The term "introduced into" is understood to mean uptake in the cell. Uptake may occur by means of the cell itself. However, it may also be mediated by auxiliary agents or devices. "Overhang" is understood to mean a single-stranded projection located at an end, which does not exhibit Watson-Crick paired nucleotides. "Double-stranded structure" is understood to mean a structure in which the nucleotides of the individual strands are generally paired in accordance with Watson & Crick. In terms of the present invention, a double-stranded structure may also exhibit individual mismatches.

In a particularly advantageous embodiment, dsRNA I exhibits the overhang at the 3'-end of the strand or antisense strand as1 and/or at the 3'-end of the other strand or antisense strand ss1. dsRNA I may also be smooth at one end. In this case, the smooth end is advantageously located on the side of dsRNA I that (exhibits)¹ the 5'-end of a strand (antisense strand; as1). In this embodiment, dsRNA I exhibits very good effectiveness as well as great stability in the living organism. Total in vivo effectiveness is outstanding. The overhang consists advantageously of 1 to 4 nucleotides, preferably of 1 or 2 nucleotides.

In accordance with a further embodiment, the effectiveness of the method can be further enhanced when at least one further dsRNA II corresponding to the dsRNA I in the invention is introduced into the cell, whereby one strand, or at least a segment of one strand of the double-stranded structure of dsRNA

¹ the word "exhibits" is missing.

I is complementary to a first region of the sense strand of the target gene, and whereby another strand, or at least a segment of the other strand of the double-stranded structure of the dsRNA II is complementary to a second region of the sense strand of the target gene. Inhibition of expression of the target gene is markedly enhanced in this case. The first and second region can overlap segmentally, be adjacent to each other, or be separated.

10 It has further been shown to be advantageous when the dsRNA I and/or the further dsRNA II is fewer than 25 successive nucleotide pairs in length. A length of between 19 and 23 nucleotide pairs has been shown to be particularly effective. Efficiency can be further enhanced when single-stranded
15 overhangs containing 1 to 4 nucleotides are present in the double strands preferably formed by 19 to 23 nucleotide pairs.

The target gene can, in accordance with a further embodiment, exhibit one of the sequences SQ001 to SQ140 shown in the
20 appended sequence protocol. It may be selected from the following group: an oncogene; cytokinin gene; Id protein gene; prion gene; gene that expresses molecules that induce angiogenesis, adhesion molecules, and cell surface receptors; genes of proteins that are involved in metastasizing and/or
25 invasive processes; genes of proteinases as well as of molecules that regulate apoptosis and the cell cycle; genes that express the EGF receptor. In particular, the target gene can be a MDR1 gene. It may be used in this connection a dsRNA I/II consisting of one of the sequences SQ141-173 or a combination of one of the
30 antisense (as) and sense sequences (ss) that belong together.

In accordance with another advantageous embodiment, expression is inhibited according to the principle of RNA interference.

The target gene is advantageously expressed in pathogenic organisms, preferably in plasmodia. It can be a component of a virus or viroid, particularly a virus or viroid that is pathogenic in humans. The virus or viroid can also be one that is pathogenic in animals or plants.

In another embodiment, it is provided that the unpaired nucleotides are substituted by nucleoside thiophosphates.

At least one end of the dsRNA I/II may be modified to counteract decomposition in the cell or dissociation in the individual strands. Advantageously, the cohesion of the double-stranded structure that results from the complementary nucleotide pairs is enhanced by at least one chemical bond. The chemical bond may be achieved either by a covalent or ionic bond, a hydrogen bond, hydrophobic interaction, preferably by means of van der Waals or stacking interactions, or by means of metal-ion coordination. In addition, it has also been shown to be advantageous and stability-enhancing if the chemical bond occurs in the vicinity of one end. Other advantageous embodiments with regard to chemical bonding can be found in the features in Claims 24 to 30, and no further explanation is required.

dsRNA I/II may be particularly easily introduced into the cell when it is enclosed in micellar structures, preferably in liposomes. For the transport of dsRNA I/II into the cell, it has been found to be advantageous that they be bound, associated, or enclosed by at least one viral coat protein that stems directly from a virus, is derived from it, or is synthetically produced. The coat protein may be derived from a polyoma virus. In particular, the coat protein may contain Virus Protein 1 and/or Virus Protein 2 of the polyoma virus. In accordance with a further embodiment, it is provided that during formation of a capsid or capsid-like structure from coat protein, one side is

turned to the interior of in the capsid or capsid-like structure. Furthermore, it is advantageous that one strand of the dsRNA I/II (as1/2) is complementary to the primary or processed RNA transcript of the target gene. The cell may be
5 either a vertebrate cell or a human cell.

Furthermore, it has been demonstrated that dsRNA I/II may be administered to mammals, preferably human beings, even at a maximum dose of 5 mg/kg body weight per day. Even at this low
10 dosage effectiveness is outstanding.

Surprisingly, it has been shown that dsRNA I/II may be mixed in a buffer solution and then administered orally or by injection or infusion, either intravenously, intratumorally,
15 intraperitoneally, or inhalationally.

Furthermore, the invention provides the use of a double-stranded ribonucleic acid (dsRNA I) to inhibit expression of a target gene in the cell, whereby dsRNA I exhibits a double-stranded
20 structure consisting of a maximum of 49 successive nucleotide pairs, and whereby one strand (antisense strand, as1) or at least one segment of the strand of the double-stranded structure is complementary to the sense strand of the target gene, and whereby dsRNA I exhibits an overhang at one end consisting of 1
25 to 4 nucleotides.

In accordance with another measure of the invention, a medicament containing one double-stranded ribonucleic acid (dsRNA I) in a quantity sufficient to inhibit expression of the
30 target gene in a cell is provided, whereby dsRNA I exhibits a double-stranded structure consisting of a maximum of 49 successive nucleotide pairs, and whereby one strand (as1) or at least one segment of one strand (as1) of the double-stranded structure is complementary to the sense strand of target gene,

and whereby the dsRNA I exhibits at least one overhang at one end consisting of 1 to 4 nucleotides.

Refer to the previous discussion for other advantageous
5 embodiments of dsRNA I/II.

The invention will be explained on the basis of drawings and examples as follows. These show:

10 Fig. 1a, b diagram of a first and second double-stranded RNA
and

Fig. 2 diagram of a target gene,

15 Fig. 3 relative YFP fluorescence after application of
various dsRNAs in NIH/3T3 cells (first experiment),

Fig. 4 relative YFP fluorescence after application of
various dsRNAs in NIH/3T3 cells (second experiment),

20 Fig. 5 relative YFP fluorescence after application of various
dsRNAs in NIH/3T3 cells (third experiment),

Fig. 6 relative YFP fluorescence after application of various
25 dsRNAs in NIH/3T3 cells (fourth experiment),

Fig. 7 relative YFP fluorescence after application of various
dsRNAs in Hela-S3 cells (fifth experiment),

30 Fig. 8 fluorescence microscopic imaging of NIH/3T3 cells
after transfection with pcDNA-YFP or after
cotransfection with pcDNA-YFP and various dsRNAs,

- Fig. 9 fluorescence microscopic imaging of HeLa-S3 cells after transfection with pcDNA-YFP or after cotransfection with pcDNA-YFP and various dsRNAs,
- 5 Fig. 10 gel electrophoretic separation of S1 after incubation in mouse serum,
- Fig. 11 gel electrophoretic separation of S1 after incubation in human serum,
- 10 Fig. 12 gel electrophoretic separation of S7 after incubation in mouse serum,
- Fig. 13 gel electrophoretic separation of S7 after incubation in human serum,
- 15 Fig. 14 gel electrophoretic separation of K3 after incubation in mouse serum,
- 20 Fig. 15 gel electrophoretic separation of PKC1/2 after incubation in mouse serum,
- Fig. 16 gel electrophoretic separation of S1A/S4B after incubation in human serum,
- 25 Fig. 17 gel electrophoretic separation of K2 after incubation in human serum, and
- Fig. 18 GFP-specific immunoperoxidase staining of kidney paraffin sections from transgenic GFP mice,
- 30 Fig. 19 GFP-specific immunoperoxidase staining of heart paraffin sections from transgenic GFP mice,

- Fig. 20 GFP-specific immunoperoxidase staining of pancreas
paraffin sections from transgenic GFP mice,
- Fig. 21 Western blot analysis of GFP expression in plasma,
- 5 Fig. 22 Western blot analysis of GFP expression in kidney,
- Fig. 23 Western blot analysis of GFP expression in heart,
- 10 Fig. 24 Western blot analysis of EGFR expression in U-87 MG
glioblastoma cells,
- Fig. 25a Northern blot analysis of the MDRI mRNA level in colon
carcinoma cell line LS174T, whereby the cells were
- 15 harvested after 74 hours,
- Fig. 25b quantification of the bands in Figure 25a, whereby the
averages are represented by two values,
- 20 Fig. 26a Northern blot analysis of the MDRI mRNA level in colon
carcinoma cell line LS174T, whereby the cells were
harvested after 48 hours,
- Fig. 26b quantification of the bands in Figure 26a, whereby the
- 25 averages of two values are represented,
- Fig. 27 comparison of a transmitted light- and fluorescence
microscopic imaging of a transfection with 175 nM
dsRNA (Sequence R1 in Table 4).

30

The double-stranded ribonucleic acids dsRNA I and dsRNA II depicted schematically in Figures 1a and 1b each exhibit a first end (E1), and a second end (E2). The first and the second ribonucleic acids dsRNA I/dsRNA II exhibit single-stranded

segments at both ends (E1, E2), being formed of approximately 1 to 4 unpaired nucleotides. Two possible variants are shown (Variants 1 and 2), whereby Variant 2 exhibits a smooth end (E2). The smooth end may, however, be situated at the other end (E1) in other variants.

Figure 2 shows schematically a target gene located on a DNA. The target gene has been made visible by means of a black line. It exhibits a first region (B1) and a second region (B2).

In each case, one strand of the first dsRNA I (as1) or of the second dsRNA II (as2) is complementary to the corresponding region B1 or B2 in the target gene, respectively.

Expression of the target gene is inhibited particularly effectively when dsRNA I/dsRNA II exhibits single-stranded segments at their ends (E1, E2). The single-stranded segments may be located both on strand as1 or as2, or on anti-strand (ss1 or ss2), or on strand as1, as2, and on the anti-strand.

Regions B1 and B2 may be separated from each other as shown in Figure 2. However, they may also adjoin or overlap.

I. Inhibition of the expression of the YFP gene in fibroblasts:

Double-stranded RNAs were derived from sequences of Yellow Fluorescent Proteins (YFP), a variant of GFP (Green Fluorescent Protein) from the *Aequoria victoria* alga, and microinjected into fibroblasts together with a YFP-coding plasmid. Subsequently, the decrease in fluorescence compared to cells without dsRNA was analyzed.

Experiment protocol:

Single RNA strands and their complementary single strands were synthesized from sequence protocols SQ148, SQ149 and SQ159,

using an RNA synthesizer (Expedite 8909, Applied Biosystems, Weiterstadt, Germany) and conventional chemical processes. These were subsequently purified using HPLC. Hybridization of the individual strands into double strands was done by heating up the stoichiometric mixture of the single strands in 10 mM of sodium phosphate buffer, pH 6.8, and 100 mM NaCl to 90°C, and then allowing it to cool off slowly for 6 hours to room temperature. The dsRNA that was obtained in this way was microinjected into the test cells.

10

The test system used for this cell culture experiment was the murine fibroblast cell line NIH/3T3, ECACC No. 93061524 (European Collection of Animal Cell Culture). The pcDNA-YFP plasmid, which contains an 800bp Bam HI/Eco RI-YFP fragment in the corresponding restriction site of the pcDNA3 vector, was used for the microinjections. Expression of YFP under the influence of simultaneously transfused sequence-homologous dsRNA was studied. Analysis of green fluorescence under the fluorescence microscope was done 3 hours after injection at the earliest.

20

Preparation of the cell cultures:

The cells were incubated in DMEM with 4.5 g/l glucose and 10% fetal calf serum (FCS), 2 mM L-glutamine, and penicillin/streptomycin (100 IU/100 µg/ml, Biochrom) in an incubator in an atmosphere containing 5% CO₂ at 37°C. The cells were passaged every 3 days in order to maintain them in an exponential growth state. One day before transfection, the cells were trypsinized (10x trypsin/TEDTA, Biochrom) and placed in coated petri dishes (CORNING Cell Culture Dish, 35 mm, Corning Inc., Corning NY) at a cell density of 0.3×10^5 . The petri dishes were incubated for at least 30 minutes at 37°C with 0.2% gelatin (Biochrom), washed once with PBS, and used immediately to

30

culture the cells. In order to find the individual cells again, CELLocate coverslips were used (square sized 55µm, Eppendorf).

Microinjection:

- 5 The petri dishes were taken out of the incubator approximately 10 minutes prior to microinjection. Approximately 50 cells per dish and per incubate were microinjected (FemtoJet, Micromanipulator 5171, Eppendorf). Glass capillaries (FemtoTip, Eppendorf) with an internal tip diameter of 0.5 µm were used.
- 10 Injection time was 0.8 seconds at a pressure of 30 hPA. Microinjection took place under an Olympus IX50 microscope equipped for fluorescence. The injection buffer used consisted of 14mM NaCl, 3 mM KCl, and 10 mM KH₂PO₄, pH 7.0, which contained 0.01 µg/µl pcDNA-YFP. An injection solution of 0.08% (w/v) Texas
- 15 red coupled with dextran 70000 (Molecular Probes, Leiden, Netherlands) was added to test for successful microinjection. In order to analyze the inhibition of YFP expression with specific dsRNA, dsRNAs were added to the injection solution: Assay 1: 0.01 µM dsRNA (sequence protocol SQ148/149); Assay 2: 0.01 µM
- 20 dsRNA (sequence protocol SQ148/159); Assay 3: without RNA. After microinjection, the cells were incubated for at least another 3 hours in an incubator. Intracellular YFP fluorescence was then analyzed under the microscope: the cells that fluoresced both red and green simultaneously: microinjection was successful, no
- 25 inhibition of YFP expression as a result of dsRNA was observed, or there were control cells into which no dsRNA was injected; only red fluorescent cells: microinjection was successful, dsRNA inhibited YFP expression.

30 Results:

At a dsRNA concentration of 0.1 µM, the use of dsRNA with single-stranded regions with two-nucleotide overhangs each at both 3'-ends (sequence protocol SQ148/159) markedly enhanced inhibition of the expression of the YFP gene in fibroblasts in

comparison to dsRNA without end having single overhanging strands (Table 1).

The use of short dsRNA molecules, containing 19-25-base pairs with overhangs consisting of a few, preferably 1 to 3, non-base-paired single-stranded nucleotides thus makes possible a comparatively more powerful inhibition of gene expression in mammalian cells than does the use of dsRNAs with the same number of base pairs without the corresponding single-stranded overhangs at the same RNA concentrations.

Assay	Name	Sequence protocol No.	0.1 μ M
1	S1A/	SQ148	+
	S1B	SQ149	
2	S1A/	SQ148 (overhanging ends)	+++
	S4B	SQ159	
3		Without RNA	-

Table 1: The symbols give the relative proportion of non- or weakly-fluorescent cells (+++ > 90%; ++ 60-90%; + 30-60%; - < 10%).

II. Inhibition by dsRNA of gene expression of a target gene in cultured HELA-S3 cells and mouse fibroblasts:

The effectiveness of the inhibition of YFP expression after transient transfection of a YFP-coding plasmid on the basis of RNA interference with dsRNA may be modulated by manipulating the 3'-ends and the length of the base-paired region.

Example:

In order to determine the effectiveness of dsRNA in the specific inhibition of gene expression, transient transfected NIH/3T3

cells (fibroblasts from NIH Swiss mouse embryo, ECCAC [European collection of animal cell culture] No. 93061524) and HELA-S3 (human cervical cancer cells, DSMZ [German collection of microorganisms and cell cultures] No. ACC 161) were used. The
5 pcDNA-YFP plasmid, containing an 800-bp Bam HI/Eco RI-YFP fragment in the corresponding cleaving sites of the vector pcDNA 3, was used for transfection. Double-stranded RNAs (dsRNAs) derived from the sequence of the yellow fluorescent protein (YFP) were produced and transiently transfected into the
10 fibroblasts along with the pcDNA-YFP plasmid (the antisense strands of the specific dsRNAs used are complementary to the corresponding segments of the gene sequences of both YFP and GFP). The reduction in fluorescence was quantified after 48 hours. Cells that were either transfected only with pcDNA-YFP or
15 with pcDNA-YFP and a control dsRNA (not derived from the YFP sequence) were used as controls.

Test protocol:

20 dsRNA synthesis:

The individual RNA strands seen in the sequence protocols as well as their complementary single strands were synthesized using an RNA synthesizer (Expedite 8909, Applied Biosystems, Weiterstadt, Germany), as well as by conventional chemical
25 means. Purification of the raw synthesis products was then done with the help of the HPLC. The NucleoPac PA-100, 9 x 250 column (Dionex) was used with 20 mM tris, 10 mM NaClO₄, pH 6.8, 10% acetonitrile were used as the low salt buffer, and 20 mM tris, 400 mM NaClO₄, pH 6.8, 10% acetonitrile were used as the high
30 salt buffer. Flow was 3 ml per minute. Hybridization of the single strands into a double-stranded was done by heating the stoichiometric mixture of the single strands in 10 mM sodium phosphate buffer, pH 6.8, and 100 mM NaCl to 80-90°C and then allowing it to cool slowly over 6 hours to room temperature.

Seeding the cells:

All cell culturing was conducted under sterile conditions at an appropriate workstation (HS18/ Hera Safe, Kendro, Heraeus).

- 5 Culturing of the NIH/3T3 cells and the HELA-S3 was done in the incubator (CO₂-incubator T20, Hera Cell, Kendro, Heraeus) at 37°C, 5% CO₂, and saturated atmospheric humidity in DMEM (Dulbecco's modified eagle medium, Biochrom) for the mouse fibroblasts, and in Ham's F12 for the HELA cells, with 10% FCS
- 10 (fetal calf serum, Biochrom), 2 mM L-glutamine (Biochrom), and penicillin/streptomycin (100 IU/100µg/ml, Biochrom). In order to maintain the cells in an exponential growth state, the cells were passaged every 3 days. Twenty-four hours before
- 15 transfection, the cells were trypsinized (10x trypsin/EDTA, Biochrom, Germany) and placed in a 96-well plate (Multiwell Schalen 96-well, flat-bottom, Schubert & Weiss Laboratories, GmbH) at a cell density of 1.0×10^4 cells/depression and cultured in 150 µl growth medium.

20 Implementation of transient transfection:

- Transfection was done using Lipofectamine Plus™ reagent (Life Technologies) in accordance with manufacturer directions. 0.15 µg pcDNA-YFP plasmid was placed in each well. The entire transfection volume was 60 µl. In each case, 3 samples were
- 25 started. First, the plasmid DNA was complexed together with the dsRNA. The plasmid DNA and dsRNA were diluted in serum-free medium, and 1 µl PLUS reagent was used per 0.1 µg of plasmid DNA (in a volume of 10 µl). This was then incubated at room
- 30 temperature after mixing for 15 minutes. During incubation 0,5 µl lipofectamine was diluted in 10µl serum-free medium per 0,1 µg plasmsid-DNA, well mixed, added to the plasmid/dsRNA/PLUS-mixture and again incubated for 15 minutes. The medium was changed during incubation. The cells were washed once with 200

µl serum-free medium, and thereafter incubated with 40 µl serum-free medium in the incubator until the addition of DNA/dsRNA/PLUS/Lipofectamine. After the addition of 20 µl DNA/dsRNA/PLUS/Lipofectamine per well, the cells were incubated in an incubator for 2.5 hrs. After incubation, the cells were washed once with 200 µl growth medium and incubated in the incubator for 24 hours in 200 µl growth medium until fluorescence detection was done.

10 Fluorescence detection:

24 hours after the last medium change, cell fluorescence was photographed using a fluorescence microscope (IX50-S8F2, ULS100Hg fluorescence unit, Brenner U-RFL-T200, Olympus) with a USH I02D mercury lamp (Ushio Inc., Tokyo, Japan), fitted with a WIB fluorescence cube and a digital CCD camera (Orca IIm, Hamamatsu), and a C4742-95 preview monitor. Analysis of the fluorescence images was done using Analysis Software 3.1 (Soft Imaging System GmbH, Germany. In order to relate YFP fluorescence to cell density, cell nucleus staining was done (Hoechst staining). For this the cells were fixed, first in 100 µl methycarnoy (75% methanol, 25% glacial acetic acid) for 5 minutes, and then again for 10 minutes in methycarnoy. After air drying, the fixed cells were incubated in the dark for 30 minutes with 100 µl Hoechst stain per well (75 ng/ml). After washing twice with PBS (Dulbecco PBS w/o Ca^{2+} , Mg^{2+} , Biochrom), the cells that had been Hoechst stained were photographed under the fluorescence microscope (Olympus, WU fluorescence cube for Hoechst).

30 The results regarding inhibition of YFP expression in cultivated cells by dsRNA are summarized in Figures 3 to 9: The effects of YFP-specific dsRNAs and of control dsRNAs on YFP expression in NIH/3T3 mouse fibroblasts after transient transfection are summarized in Figures 3, 4, 5, and 6. The experiments were

carried out as described in the test protocol. The concentration of dsRNA relates to the concentration in the medium during the transfection reaction. The dsRNA designations may be seen in Table 2. It shows the relative fluorescence per photographic
5 image in terms of surface percentage. Three different photographic images were analyzed per well. The average values are obtained from the three images.

Specific inhibition of YFP-gene expression by dsRNAs in HELA-S3
10 cells is shown in Figures 7 and 9. Figure 7 shows the inhibiting action of variously configured dsRNA constructs (Table 2) in various concentrations on expression of YFP in HeLa cells. Figure 8 shows representative fluorescence microscopic images of NIH/3T3 mouse fibroblasts transiently transfected with YFP,
15 without dsRNA and with specific anti-YFP-directed dsRNAs (100x enlargement).

8A: YFP control

8B: S1, 10 nM

20 8C: S4, 10 nM

8D: S7, 10 nM

8E: S7/S11, 1 nM

8F: S7/S12, 1 nM

25 Figure 9 shows representative fluorescence microscopic images of HELA-3S cells transiently transfected with YFP, without dsRNA and with specific anti-YFP-directed dsRNAs (100x enlargement).

9A: K2 control, 10 nM

9B: S1, 10 nM

30 9C: S4, 10 nM

9D: S7, 10 nM

9E: S7/11, 1 nM

9F: S7/12, 1 nM

9G: S1A/S4B, 10 nM

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9H: YFP control

Results:

5 Figure 3 shows that YFP expression after transient
cotransfection of mouse fibroblasts with the YFP plasmid and
specific anti-YFP-sequence-directed dsRNAs can be particularly
effectively inhibited when the 3'-ends of the 22- and 19-base-
pair-containing regions of the dsRNAs exhibit single-stranded
10 segments of 2 nucleotides (nt). Whereas the S1 dsRNA with smooth
3'-ends exhibits no inhibitory effects on YFP expression at a
concentration of 1 nM (relating to the concentration in the cell
culture medium during transfection), the S7 dsRNA (19 nucleotide
pairs) and the S4 (22 nucleotide pairs), each with 2nt overhangs
15 at both 3'-ends, inhibited YFP expression by 50% and 70%,
respectively, in comparison to the corresponding control dsRNAs
(K3 and K2). At a concentration of 10 nM, the dsRNA with the
smooth ends designated S1 inhibits YFP expression by ~65%,
whereas the S4 dsRNA inhibits YFP expression by ~93% (Figure 4).
20 The inhibitory effects of the dsRNAs designated as S4 and S7 are
concentration-dependent (Figure 3 and 4; see also Figure 7).

Figure 4 shows that the single-stranded configuration at both
3'-ends (of the sense and antisense strand) is not necessary for
25 efficient suppression of YFP gene expression. To achieve
effective inhibition of YFP expression, only the 2nt overhang at
the 3'-end of the antisense strand is necessary. Thus, for both
S4 dsRNAs (with 2nt overhangs at both 3'-ends) and S1A/S4B (with
one 2nt overhang at the 3'-end of the antisense strand)
30 inhibition of YFP expression at a concentration of 1 nM is ~70%.
However, if on the other hand the 2nt overhang is located at the
3'-end of the sense strand (and the 3'-end of the antisense
strand does not have a single-stranded region), inhibition of

YFP gene expression is 50%. Analogously, inhibition at higher concentrations is considerably better when at least the 3'-end of the antisense strand has a 2nt overhang.

- 5 A more marked inhibition of YFP expression is achieved when the base-paired region has 21 nucleotide pairs instead of 22 (S1 and S4), 20 (S13 or S13/14, or 19 (S7) (Figures 5, 6, and 7). Thus, at a concentration of 5 nM, inhibition of YFP expression by S1 (22 base pairings with smooth ends) is ~40%, while inhibition by
10 S7/S12 (21 base pairings with smooth ends), also at 5 nM, is ~92%. If the dsRNA with 21 base pairings exhibits another 2nt overhang at the antisense strand 3'-end (S7/S11), inhibition is ~97% (compared with ~73% inhibition by S4 and ~70% inhibition by S7).

15

III. Analysis of serum stability of double-stranded RNA (dsRNA):

- The object is to take the effectiveness of the inhibition on the gene expression of target genes mediated by dsRNAs found in cell
20 cultures and enhance it for use in vivo. This is achieved by improving the stability of dsRNA in serum, and by increasing the retention time of the molecule in the blood circulation, or by increasing the effective concentration of the functional molecule that results from the foregoing.

25

Example:

Serum stability of GFP-expression-inhibiting dsRNAs was tested ex vivo in murine and human serum.

30 Test protocol:

Incubation of human and murine serum with corresponding dsRNA was done at 37°C. In each case, 85µl serum was incubated with 15

µl 100µM dsRNA. After certain incubation spans (30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours) the samples were frozen at -80°C. DsRNA without serum (+85 µl ddH₂O) and dsRNA with serum at Time 0 were used as controls.

5

In order to isolate dsRNA from the incubate, which was done on ice, 400 µl 0.1% SDS was added to each incubate, and these then underwent phenol extraction: 500 µl phenol:chloroform:isoamyl alcohol (IAA, 25:24:1, Roti phenol, Roth, Karlsruhe) were added
10 to each incubate, and then vortexed at the highest setting for 30 seconds (Vortex Genie-2, Scientific Industries). After incubation for 10 minutes on ice, phase separation was carried out by centrifugation at 12,000 xg at 4°C for 10 minutes (Sigma 3K30, Rotor 12131-H). The top aqueous phase (approximately 200
15 µl) was collected and then underwent digestion: first with DNase I and then with Proteinase K: 20 µl 10x DNase buffer (100 mM tris, pH 7.5, 25 mM MgCl₂, 1 mM CaCl₂) and 10 U DNase I (D 7291, Sigma-Aldrich) were added incubated for 30 minutes at 37°C, then 6 U DNase I were again added, incubated for another 20 minutes
20 at 37°C. Then 5µl Proteinase K (20 mg/ml, 04-1075, Peglabs, Germany) was added and incubated for 30 minutes at 37°C. Phenol extraction was then carried out. To this was added 500 µl phenol:chloroform:IAA (25:24:1), vortexed for 30 seconds at the highest setting, and then centrifuged for 10 minutes at 12,000
25 xg and 4°C. The supernatant fluid was drawn off and replaced sequentially with 40 µl 3 M Na-Ac (sodium acetate), pH 5.2, and 1 ml 100% EtOH; this was well mixed and precipitated for at least one hour at -80°C. The precipitate was pelleted by centrifugation at 12,000 xg for 30 minutes at 4°C, washed with
30 70% EtOH, and again centrifuged (10 minutes, 12,000 xg at 4°C). The air-dried pellet was then mixed in 30 µl RNA gel application buffer (7 M urea, 1 x TBE [0.09 M tris borate, 0.002 M EDTA, 0.02% [w/v] bromophenol blue, 0.2% [w/v] xylencyanol) and stored at -20°C until gel application.

In order to characterize the dsRNA, analytic, denaturing polyacrylamide gel electrophoresis (analytic PAGE) was carried out. The urea gels were produced shortly before the run: 7M urea (21 g) was dissolved while stirring in 25 ml 40% aqueous acrylamide/bisacrylamide solution (Rotiphoresis gel, A515.1, Roth) and 5 ml 10 x TBE (108 g tris, 55 g boric acid, 3.9 g EDTA per liter distilled water) and diluted to 50 ml with of distilled water. Shortly before pouring, 50 µl TEMED (N,N,N',N'-tetramethyl ethylendiamine) and 500 µl 10% APS (ammonium peroxide sulfate) were added. After polymerization, the gel was placed in a vertical electrophoresis apparatus (Merck, Darmstadt), and a first fraction was carried out for 30 minutes at a constant amperage of 40 mA. 1 x TBE buffer was used as the running buffer. Before applying them to the gel, the RNA samples were heated for 5 minutes at 100°C, cooled on ice, and then centrifuged for 20 seconds on a table centrifuge (Eppendorf Minispin). 15 µl of each sample was applied to the gel. The test run lasted for approximately two hours at a constant amperage of 40 mA. After the run, the gel was stained with Stains All staining solution (20 ml Stains All solution [200 mg Stains All dissolved in 200 ml formaldehyde] with 200 ml of distilled water and 100 ml formamide), and the background stain was then removed by rinsing with distilled water for 45 minutes. The gels were photographed using the Image Master VDS photodocumentation system from Pharmacia. Figures 10 to 17 show the serum stability of dsRNA after incubation with human or murine serum, and subsequent electrophoretic separation in 20% 7M urea gel.

Figure 10: Incubation of S1 (0-22-0) in mouse serum

1. At Time 0 (without serum)
2. At Time 0
3. For 30 minutes
4. For 1 hour
5. For 2 hours

6. For 4 hours
7. For 12 hours
8. 2 μ l 100 μ M S1 without incubation
- S1A) sense strand S1 (10 μ l 20 μ M S1A)
- 5 S1B) antisense strand S1 (10 μ l 20 μ M S1B)

Figure 11: Incubation of S1 (0-22-0) in human serum

1. 2 μ l 100 μ M S1 untreated (without incubation)
2. For 30 minutes
3. For 2 hours
- 10 4. For 4 hours
5. For 6 hours
6. For 8 hours
7. For 12 hours
8. For 24 hours
- 15 S1A) sense strand S1 (10 μ l 20 μ M S1A)
- S1B) antisense strand S1 (10 μ l 20 μ M S1B)

Figure 12: Incubation of S7 (2-19-2) in mouse serum

1. At Time 0 (without serum)
2. For 30 minutes
3. For 4 hours
- 5 4. For 12 hours

Figure 13: Incubation of S7 (2-19-2) in human serum

1. Sense strand S7 (10 µl 20 µM S7A)
2. Antisense strand S7 (10 µl 20 µM S7B)
3. For 30 minutes
- 10 4. For 1 hour
5. For 2 hours
6. For 4 hours
7. For 6 hours
8. For 12 hours
- 15 9. For 24 hours
10. At Time 0 (without serum)

Figure 14: Incubation of K3 (2-19-2) in mouse serum

1. Sense strand K3 (10 µl 20 µM K3A)
2. Antisense strand K3 (10 µl 20 µM K3B)
- 20 3. At Time 0 (without serum)
4. At Time 0 (with serum)
5. For 30 minutes
6. For 1 hour
7. For 2 hours
- 25 8. For 4 hours
9. For 12 hours

Figure 15: Incubation of PKC1/2 (0-22-2) in mouse serum

1. For 30 minutes
2. For 1 hour
- 30 3. For 2 hours
4. For 4 hours
5. For 12 hours
6. 2 µl 100µM PKC1/2 (untreated)

Figure 16: Incubation of S1A/S4B (0-22-2) in human serum

1. At Time 0 (without serum)
2. For 24 hours
3. For 12 hours
- 5 4. For 8 hours
5. For 6 hours
6. For 4 hours
7. For 2 hours
8. For 30 minutes
- 10 9. Sense strand S1A (10 μ l 20 μ M S1A)
10. Antisense strand S4B (10 μ l 20 μ M S4B)

Figure 17: Incubation of K2 (2-22-2) in human serum

1. Sense strand K2 (10 μ l 20 μ M K2A)
2. Antisense strand K2 (10 μ l 20 μ M K2B)
- 15 3. At Time 0 (without serum)
4. For 30 minutes
5. For 2 hours
6. For 4 hours
7. For 6 hours
- 20 8. For 8 hours
9. For 12 hours
10. For 24 hours

Results:

25 DsRNAs without single-stranded regions at the 3'-ends are considerably more stable in both human and mouse serum than are dsRNAs with single-stranded 2nt overhangs at the 3'-ends (Figures 10 to 14 and 17). After 12 and 24 hours, respectively,

30 of incubation of S1 in both murine and human serum, one band of the original size remains almost completely intact. By contrast, the stability of dsRNAs with 2nt overhangs at both 3'-ends decreases considerably in both human and murine serum. Even

after only 4 hours of incubation of S7 (Figures 12 and 13) or K3 (Figure 14), no band of the original size is still detectable.

In order to enhance the stability of dsRNA in serum, it is sufficient if the dsRNA possesses one smooth end. The original size of the band has hardly been broken down at all in mouse serum after 4 hours incubation (Figure 15, Track 4) when compared to S7 (complete decomposition after 4 hours; Figure 12, Track 3)

10

One optimal compromise with regard to the biological effectiveness of dsRNA may be the use of dsRNA with one smooth end and one single-stranded region of 2 nucleotides, whereby the single-stranded overhang is located at the 3'-end of the antisense strand.

15

The sequences used here are reproduced in the following Table 2 and in the sequence protocols SQ148-151 and 153-167.

Name	Sequence protocol No.	dsRNA-Sequence	
S1	SQ148 SQ149	(A) 5'- CCACAUGAAGCAGCACGACUUC -3' (B) 3'- GGUGUACUUCGUCGUGCUGAAG -5'	0-22-0
S7	SQ150 SQ151	(A) 5'- CCACAUGAAGCAGCACGACUU -3' (B) 3'- CUGGUGUACUUCGUCGUGCUG -5'	2-19-2
K1	SQ153 SQ154	(A) 5'- ACAGGAUGAGGAUCGUUUCGCA -3' (B) 3'- UGUCCUACUCCUAGCAAAGCGU -5'	0-22-0
K3	SQ155 SQ156	(A) 5'-GAUGAGGAUCGUUUCGCAUGA-3' (B) 3'-UCCUACUCCUAGCAAAGCGUA-5'	2-19-2
K2	SQ157	(A) 5'- ACAGGAUGAGGAUCGUUUCGCAUG -3'	

	SQ158	(B)	3' - UCUGUCCUACUCCUAGCAAAGCGU -5'	2-22-2
S1A/ S4B	SQ148	(A)	5' - CCACAUGAAGCAGCACGACUUC -3'	0-22-2
	SQ159	(B)	3' - CUGGUGUACUUCGUCGUGCUGAAG -5'	
PKC 1/2	SQ160	(A)	5' - CUUCUCCGCCUCACACCGCUGCAA -3'	2-22-0
	SQ161	(B)	3' - GAAGAGGCGGAGUGUGGCGACG -5'	
S7/S12	SQ150	(A)	5' - CCACAUGAAGCAGCACGACUU -3'	0-21-0
	SQ162	(B)	3' - GGUGUACUUCGUCGUGCUGAA -5'	
S7/S11	SQ150	(A)	5' - CCACAUGAAGCAGCACGACUU -3'	0-21-2
	SQ163	(B)	3' - CUGGUGUACUUCGUCGUGCUGAA -5'	
S13	SQ164	(A)	5' - CCACAUGAAGCAGCACGACU -3'	0-20-2
	SQ165	(B)	3' - CUGGUGUACUUCGUCGUGCUGA -5'	
S13/14	SQ164	(A)	5' - CCACAUGAAGCAGCACGACU -3'	0-20-0
	SQ166	(B)	3' - GGUGUACUUCGUCGUGCUGA -5'	
S4	SQ167	(A)	5' - CCACAUGAAGCAGCACGACUUCUU -3'	2-22-2
	SQ159	(B)	3' - CUGGUGUACUUCGUCGUGCUGAAG -5'	
K1A/ K2B	SQ153	(A)	5' - ACAGGAUGAGGAUCGUUUCGCA -3'	0-22-2
	SQ158	(B)	3' - UCUGUCCUACUCCUAGCAAAGCGU -5'	
K1B/ K2A	SQ154	(A)	5' - ACAGGAUGAGGAUCGUUUCGCAUG -3'	2-22-0
	SQ157	(B)	3' - UGUCCUACUCCUAGCAAAGCGU -5'	
S1B/ S4A	SQ149	(A)	5' - CCACAUGAAGCAGCACGACUUCUU -3'	2-22-0
	SQ167	(B)	3' - GGUGUACUUCGUCGUGCUGAAG -5'	

Table 2

IV. In vivo study:

5

Double-stranded RNA (dsRNA) that was derived from the GFP sequence and nonspecific dsRNA, respectively, was injected into

the caudal vein of "GFP lab mice" that express the green fluorescent protein (GFP) in all cells that are involved in protein biosynthesis. At the end of the experiment the animals were killed and tissue sections and plasma GFP expression were
5 analyzed.

Test protocol:

dsRNA synthesis:

10 The individual RNA strands seen in the sequence protocols as well as their complementary individual strands were synthesized using an RNA synthesizer (Expedite 8909, Applied Biosystems, Weiterstadt, Germany), as well as by conventional chemical means. Purification of the raw synthesis products was then done
15 with the help of the HPLC. The NucleoPac PA-100, 9 x 250 column (Dionex) was used: 20 mM tris, 10 mM NaClO₄, pH 6.8, 10% acetonitrile was used as the low salt buffer, and 20 mM tris, 400 mM NaClO₄, pH 6.8, 10% acetonitrile was used as the high salt buffer. Flow was 3 ml per minute. Hybridization of the
20 individual strands into a double-stranded was done by heating the stoichiometric mixture of the individual strands in 10 mM sodium phosphate buffer, pH 6.8, 100 mM NaCl to 80-90°C and then allowing it to cool slowly over 6 hours to room temperature.

25 Test-animal conditions and course of the experiment:

The transgenic laboratory mouse strain TgN(GFPU)5Nagy (Jackson Laboratory, Bar Harbor, ME) was used; this strain has been shown to express GFP (with a beta-actin promoter and a CMV intermediate early enhancer) in all previously tested cells,
30 (Hadjantonakis AK et al., 1993, Mech Dev. 76:79-90; Hadjantonakis AK et al., 1998, Nature Genetics 19: 220-222). The GFP-transgenic mice may be readily differentiated from the corresponding wild type (WT) on the basis of fluorescence (using a hand-held UV lamp). The corresponding WT was always paired

with a heterozygote GFP type for purposes of breeding. The experiment was conducted in accordance with the German animal rights laws. The animals were kept in a controlled environment in groups of 3-5 animals in Type III Makrolon cages (Ehret,
5 Emmendingen) at a constant temperature of 22°C and a day/night rhythm of 12 hours. Wood shavings of 8/15 granulated softwood (Altomin, Lage) were used. The animals received tap water and standard feed (Altomin 1324 pellets) ad libitum.

10 The heterozygote GFP animals that were used in the experiment were kept in cages in groups of 3 animals as described above. Injection of dsRNA solution was done intravenously (i.v.) in the caudal vein in 12-hour cycles (between 5:30 and 7:00 and between 17:30 and 19:00) over a 5-day period. Injection volume was 60 µl
15 per 10 g of body weight, and the dosage was 2.5 mg dsRNA or 50 µg, respectively, per kg body weight. The groups were divided as follows:

- 20 Group A: PBS (phosphate buffered saline) 60 µl per 10 g body weight each,
- Group B: 2.5 mg per kg body weight of a nonspecific control dsRNA (K1 control with smooth ends and a double-stranded region consisting of 22 nucleotide
25 pairs),
- Group C: 2.5 mg per kg body weight of another nonspecific control dsRNA (K3 control with 2nt overhangs at both 3'-ends and a double-stranded region
30 consisting of 19 nucleotide pairs),
- Group D: 2.5 mg per kg body weight dsRNA (specific anti-GFP directed, henceforth referred to as S1, with

smooth ends and a double-stranded region consisting of 22 nucleotide pairs),

- Group E: 2.5 mg dsRNA per kg body weight (specific anti-GFP, henceforth referred to as S7, with 2nt overhangs at the 3'-ends of both strands and a double strand region consisting of 19 nucleotide pairs),
- 10 Group F: 50 µg S1 dsRNA per kg body weight (in other words 1/50 of the dosage in Group D).

After the last of a total of 10 injections, the animals were killed after 14-20 hours, and the organs and blood were removed as described.

Organ removal:

Immediately after the animals were killed by means of CO₂ inhalation, their blood and various organs were removed (thymus, along, heart, spleen, stomach, intestines, pancreas, brain, kidneys, and liver). The organs were quickly rinsed with cold, sterile PBS and sectioned using a sterile scalpel. One portion was fixed for 24 hours in methyl carnoys (MC, 60% methanol, 30% chloroform, 10% glacial acetic acid) for immunohistochemical staining; one portion was immediately flash-frozen in liquid nitrogen and stored at -80°C for making frozen sections and for protein isolation; and another, smaller portion, was frozen in RNAeasy Protect (Qiagen) at -80°C for RNA isolation. Immediately after removal, the blood was placed on the ice for 30 minutes, mixed, and centrifuged for 5 minutes at 2000 rpm (Mini spin, Eppendorf). The supernatant fluid (here referred to as plasma) was drawn off and stored at -80°C.

Processing the biopsies:

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After the tissues had been fixed for 24 hours in MC, the tissue pieces were dehydrated in an ascending alcohol series at room temperature: 40 minutes each, 70% methanol, 80% methanol, 2 x 96% methanol and 3 x 100% isopropanol. After that, the tissue was warmed in an incubator in 100% isopropanol at 60°C, after which it was incubated for one hour in an isopropanol/paraffin mixture at 60°C and 3x for 2 hours in paraffin, and then bedded in paraffin. For the immunoperoxidase stains, the tissue sections 3 µm in thickness were prepared, using a rotation microtome (Leica), placed on glass slides (Superfrost, Vogel) and incubated for 30 minutes in an incubator at 60°C.

Immunoperoxidase staining for GFP:

The sections were deparaffinized 3 x 5 minutes in xylol, rehydrated in a descending alcohol series (3 x 3 min., 100% ethanol, 2 x 2 min. 95% ethanol), and then incubated in 3% H₂O₂/methanol to block endogenous peroxidases. All incubation steps in the following were carried out in a moist chamber. After washing with PBS 3 x 3 minutes, incubation was carried out with the first antibody (goat anti-GFP, sc-5384, Santa Cruz Biotechnology) 1:500 in 1% BSA/PBS overnight at 4°C. Incubation with the biotinylated secondary antibody (donkey anti-goat; Santa Cruz Biotechnology; dilution 1:2000) was then carried out for 30 minutes at room temperature, after which it was incubated with Avidin D peroxidase (dilution 1:2000, Vector Laboratories). After each antibody incubation, the sections were washed in PBS for 3 x 3 minutes, and the buffer residue and cell debris were removed from the sections. All antibodies were diluted in 1% bovine serum albumin (BSA)/PBS. Staining with 3,3'-diaminobenzadine (DAB) was done using a DAB substrate kit (Vector Laboratories) in accordance with manufacturer instructions. Gill's Hematoxylin III was used for the nucleic counter stain (Merck). After dehydration in an ascending alcohol series and 3 x 5 minutes xylol, the sections were covered with

Entellan (Merck). Microscopic analysis of the stains was done using an Olympus IX50 microscope fitted with a CCD camera (Hamamatsu).

5 Protein isolation from tissue pieces:

800 µl isolation buffer (50mM HEPES, pH 7.5; 150 mM NaCl; 1 mM EDTA; 2.5 mM EGTA; 10% glycerol; 0.1% Tween; 1 mM DDT; 10 mM β-glycerol phosphate; 1 mM NaF; 0.1mM Na₃VO₄ with a "Complete" protease inhibitor tablet manufactured by Roche) was added to
10 each of the still-frozen tissue pieces, and then homogenized 2 x 30 seconds using an Ultraturrax (DIAX 900, 6G disperser, Heidolph), and cooled on ice between homogenization steps. After incubation on ice for 30 minutes, it was mixed and centrifuged for 20 minutes at 10,000 xg, at 4°C (3K30, Sigma). The
15 supernatant fluid was then again incubated on ice for 10 minutes, mixed, and centrifuged for 20 minutes at 15,000 xg. Protein determination was then done on the supernatant fluid according to Bradford, 1976, modified according to Zor & Selinger, 1996, using the Roti-Nanoquant system from Roth, in
20 accordance with the manufacturer instructions. BSA (bovine serum albumin) was used for protein calibration at concentrations ranging from 10 to 100 µg/ml.

SDS gel electrophoresis:

25 Electrophoretic separation of the proteins was done in a Multigel-Long electrophoresis chamber from Biometra with a denaturing, discontinuous 15% SDS-PAGE (polyacrylamide gel electrophoresis) according to Lämmli (Nature 277: 680-685, 1970). On top of this was poured a separation gel to a thickness
30 of 1.5 mm: 7.5 ml acrylamide/bisacrylamide (30%, 0.9%), 3.8 ml 1.5 M tris/HCl, pH 8.4, 150 µl 10% SDS, 3.3 ml bidistilled water, 250 µl ammonium persulfate [10%], 9 µl TEMED (N,N,N',N'-tetramethylethylenediamine) and layered with 0.1% SDS until polymerization occurred. Then the collection gel was poured:

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0.83 µl acrylamide/bisacrylamide (30%/0.9%), 630 µl 1 M tris/HCl, pH 6.8, 3.3 ml bidistilled water, 50 µl 10% SDS, 50 µl 10% ammonium persulfate, 5 µl TEMED.

- 5 Before being applied to the gel, a corresponding quantity of 4x sample buffer (200 mM tris, pH 6.8, 4% SDS, 100 mM DTT [dithiotreitol], 0.02% bromphenol blue, 20% glycerin) was added to the proteins, and denatured on a heat block at 100°C. After cooling off on ice, this was quickly centrifuged and applied to
10 the gel. The same amounts of plasma or protein were used for each track (3 µl plasma or 25 µg total protein). Hydro-cooled electrophoresis was done at room temperature and at a constant 50 V. The protein gel marker from BioRad (Kaleidoscope Pre-stained Standard) was used as the standard length.

15

Western blot and Immunodetection:

- Transfer of the proteins from SDS-PAGE to a PVDF (polyvinyl difluoride) membrane (Hybond-P, Amersham) was done using a semidry method according to Kyhse-Anderson (J. Biochem. Biophys.
20 Methods 10:203-210, 1984) at room temperature and a constant amperage of 0.8 mA/cm² for 1.5 hours. A tris/glycine buffer (39 mM Gly, 46 mM tris, 0.1% SDS, and 20% methanol) was used as the transfer buffer. In order to analyze electrophoretic transfer, both the post-blot gels and the blot membranes were stained
25 after immunodetection using Coomassie (0.1% Coomassie G250, 45% methanol, 10% glacial acetic acid). The blot membrane was incubated after transfer in 1% skim milk powder/PBS for one hour at room temperature in order to saturate nonspecific bonds. After that, it was washed three times for 3 minutes with 0.1%
30 Tween-20/PBS. All subsequent antibody incubations and washings were done using 0.1% Tween-20/PBS. Incubation with the primary antibody (goat anti-GFP, sc-5384, Santa Cruz Biotechnology) was done at a dilution of 1:1000 for 1 hour at room temperature.

After that, it was washed 3 x 5 minutes , labeled with the

secondary antibody (donkey anti-goat IgG horseradish peroxidase, Santa Cruz Biotechnology) for 1 hour at room temperature at a dilution of 1:10,000. Detection was then done using the ECL system from Amersham in accordance with the manufacturer
5 instructions.

Figures 18 to 20 show on, 3- μ m paraffin sections, the inhibition of GFP expression after intravenous injection of specific anti-GFP directed dsRNA with anti-GFP immunoperoxidase stain. In the
10 test run, anti-GFP directed dsRNA with a double-stranded region consisting of 22 nucleotide pairs without overhangs at the 3'-ends (D) and the corresponding nonspecific control dsRNA (B), as well as the specific anti-GFP directed dsRNA with a double-stranded region comprising 19 nucleotide pairs with 2nt
15 overhangs at the 3'-ends (E) and the corresponding nonspecific control dsRNA (C) were applied in 12-hour rotations over 5 days. (F) received 1/50 of the dosage of Group D. Animals that received no dsRNA (A) and WT animals were also tested as a further control. Figure 18 shows the inhibition of GFP
20 expression in kidney sections, Figure 19 in heart tissue sections, and Figure 20 in pancreas tissue. Western blot analyses of GFP expression in plasma and tissue are shown in Figures 21 to 23. Figure 21 shows the inhibition of GFP expression in plasma; Figure 22 in kidney tissue, and Figure 23
25 in heart tissue. The application of total protein isolates from various animals is shown in Figure 23. The same amounts of total protein were applied to each track. In the animals that received nonspecific control dsRNA (animals in Groups B and C), GFP expression was not reduced in comparison to animals that
30 received no dsRNA whatsoever. Animals that received specific anti-GFP directed dsRNA that contained 2nt overhangs at the 3'-ends of both strands and a double-stranded region consisting of 19 nucleotide pairs showed significant inhibition of GFP expression in the tissues examined (heart, kidneys, pancreas,

and blood), compared with untreated animals (Figures 18 to 23). In animals in Groups D and F that were given specific anti-GFP directed dsRNA with smooth ends and a double-stranded region comprising 22 nucleotide pairs, only those animals that received
 5 the dsRNA in a dosage of 50 µg/kg body weight per day exhibited a specific inhibition of GFP expression, which, however, was less marked than in the animals in Group E.

Summary analysis of GFP inhibition in tissue sections and on
 10 Western blot show that inhibition of GFP expression is strongest in the blood and kidneys (Figures 18, 21, and 22).

V. Inhibition of gene expression of the EGF receptor with dsRNA as a therapeutic approach to forms of cancer characterized by
 15 EGFR overexpression or EGFR-induced proliferation:

The epidermal growth factor (=EGF) receptor (=EGFR) belongs to the tyrosin kinase receptors, transmembrane proteins with an intrinsic tyrosin kinase activity that are involved in the
 20 control of a series of cellular processes such as cell growth, cell differentiation, migratory processes, and cell vitality (overview in: Van der Geer et al., 1994). The EGFR family consists of 4 members, EGFR (ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) with a transmembrane domain, a cystein-rich
 25 extracellular domain, and a catalytic intracellular domain. The EGFR sequence, a 170-kDa protein, has been known since 1984 (Ullrich et al., 1984).

EGFR is activated by peptide growth factors such as EGF, TGFα
 30 (transforming growth factor), amphiregulin, betacellulin, HB-EGF (heparin binding EGF-like growth factor), and neuregulins. Ligand binding induces the formation of homodimers or heterodimers with subsequent autophosphorylation of cytoplasmic tyrosine (Ullrich & Schlessinger, 1990; Alroy & Yarden, 1997). The

phosphorylated amino acids form the binding sites of numerous proteins that are involved in the proximal stages of signal transmission in a complex network. EGFR is involved in the most varied tumoral diseases, and is therefore an appropriate target for therapeutic approaches (Huang & Harari, 1999). The mechanisms that lead to aberrant EGFR activity may be related to overexpression, amplification, constitutive activation of mutant receptor forms, or autocrine loops (Voldberg et al., 1997). Overexpression of EGFR has been described for a series of tumors such as breast cancer (Walker & Dearing, 1999), non-minor lung cancer (Fontaninii et al., 1998), pancreatic cancer, colon cancer (Salomon et al., 1995), and glioblastoma (Rieske et al., 1998). For malignant glioblastoma, in particular, there have to date been no effective and specific therapeutic agents.

Example:

To detect the effectiveness of dsRNA in the specific inhibition of EGFR gene expression, U-87 MG cells (human glioblastoma cells), ECCAC (European Collection of Animal Cell Culture) No. 89081402 was used, and was transfected with the specific anti-EGF-receptor-directed dsRNA (sequence protocol SQ 51). After approximately 72 hours of incubation, the cells were harvested, the protein was isolated, and EGFR expression was analyzed by Western blot.

Test protocol:

dsRNA synthesis:

The individual RNA strands seen in the sequence protocols as well as their complementary individual strands were synthesized using an RNA synthesizer (Expedite 8909, Applied Biosystems, Weiterstadt, Germany), as well as by traditional chemical means. Purification of the raw synthesis products was then done with

the help of the HPLC. The NucleoPac PA-100, 9 x 250 column (Dionex) was used with 20 mM tris; 10 mM NaClO₄, pH 6.8, 10% acetonitrile was used as the low salt buffer, and 20 mM tris, 400 mM NaClO₄, pH 6.8, 10% acetonitrile were used as the high salt buffer. Flow was 3 ml per minute. Hybridization of the individual strands into a double-stranded was done by heating the stoichiometric mixture of the individual strands in 10 mM sodium phosphate buffer, pH 6.8, 100 mM NaCl to 80-90°C and then allowing them to cool slowly over 6 hours to room temperature.

10

Seeding the cells:

All cell culturing was done under sterile conditions at an appropriate workstation (HS18/ Hera Safe, Kendro, Heraeus). Culturing of the U-87 MG cells was done in the incubator (CO₂-incubator T20, Hera Cell, Kendro, Heraeus) at 37°C, 5% CO₂ and saturated atmospheric humidity in DMEM (Dulbecco's modified eagle medium, Biochrom) with 10% FCS (fetal calf serum, Biochrom), 2 mM L-glutamine (Biochromone) mM sodium pyruvate (Biochrom), 1 x NEAA (nonessential amino acids, Biochrom), and penicillin/streptomycin (100 IU/100µg/ml, Biochrom). In order to maintain the cells in an exponential growth state, the cells were passaged every 3 days. 24 hours before dsRNA application by means of transfection, the cells were trypsinized (10 x trypsin/EDTA, Biochrom, Germany) and placed in a 6-well plate (6-well plates, Schubert & Weiss Laboratories, GmbH) in 1.5 µl growth medium.

25

DsRNA application in cultured U-87 MG cells:

Application of dsRNA was done by means of transfection using the OLIGOFECTAMINE™ reagent (Life Technologies) in accordance with the manufacturer instructions. Total transfection volume was 1 ml. First, the dsRNA was diluted in serum-free medium: 0.5µl of a 20 µM stock solution of specific anti-EGFR directed dsRNA and 9.5 µl of a 20 µM stock solution of nonspecific dsRNA (K1A/K2B)

30

diluted with 175 µl serum-free medium (200 nM dsRNA in the transfection incubate or 10 nM specific EGFR-dsRNA) per well. The OLIGOFECTAMINE™ reagent was also diluted in serum-free medium: 3 µl with 12 µl medium per well and then incubated for 10 minutes at room temperature. Then the diluted OLIGOFECTAMINE™ reagent was added to the medium of diluted dsRNA, mixed, and incubated for another 20 minutes at room temperature. The medium was changed during incubation. The cells were washed 1 x with 1 ml serum-free medium and continued to be incubated in the incubator with 800 µl serum-free medium until the dsRNA/OLIGOFECTAMINE™ reagent was added. After the addition of 200 µl dsRNA/OLIGOFECTAMINE™ reagent per well, the cells continued to be incubated in the incubator until protein isolation.

15 Protein isolation:

Approximately 72 hours after transfection, the cells were harvested and the protein was isolated. The medium was removed, and the cell monolayer was washed once with PBS. After the addition of 200 µl protein isolation buffer (1x "Complete" protease inhibitor, Roche, 50 mM HEPES, pH 7.5, 150 mM NaCl, 1 mM EDTA, 2.5 mM EGTA, 10% glycerin, 0.1% Tween-20, 1 mM DTT, 10 mM β-glycerine phosphate, 1 mM NaF, 0.1 mM Na₃VO₄) the cells were removed with the help of a cell scraper, incubated for 10 minutes on ice, transferred to an Eppendorf reagent vessel, and stored at -80°C for at least 30 minutes. After thawing, the lysate was homogenized at the third setting for 10 seconds with a disperser (DIAX 900, 6G disperser, Heidolph Instruments GmbH, Schwabach), incubated on ice for 10 minutes, and then centrifuged for 15 minutes at 14,000 xg at 4°C (3K30, Sigma).

30 Protein determination according to Bradford was done on the supernatant fluid using the Roti-Nanoquant system from Roth (Roth GmbH, Karlsruhe) in accordance with the manufacturer's instructions. 200 µl protein solution at a suitable dilution is mixed with 800 µl 1x working solution, and extinction was

measured in semi-microcuvettes at 450 nm and 590 nm against distilled water in a Beckman spectrophotometer (DU 250). BSA dilutions were used for calibration (beaded BSA, Sigma).

5 SDS gel electrophoresis:

Electrophoretic separation of the proteins was done in a Multigel-Long electrophoresis chamber from Biometra with a denaturing, discontinuous 7.5% SDS-PAGE (polyacrylamide gel electrophoresis) according to Lämmli (Nature 277: 680-685, 10 1970). On top of this was poured a separation gel to a thickness of 1.5 mm: 3.75 ml acrylamide/bisacrylamide (30%, 0.9%), 3.8 ml 1 M tris/HCl, pH 8.4, 150 µl 10% SDS, 7.15 ml distilled water, 150 µl ammonium persulfate (10%), 9 µl TEMED (N,N,N',N'-tetramethylethylenediamine) and layered with 0.1 percent SDS until 15 polymerization occurred. After that, the collection gel was poured: 0.83 ml acrylamide/bisacrylamide (30%/0.9%), 630 µl 1 M tris/HCl, pH 6.8, 3.4 ml distilled water, 50 µl 10% SDS, 50 µl 10% ammonium persulfate, 5 µl TEMED.

20 Before being applied to the gel, a quantity of 4x sample buffer (200 mM tris, pH 6.8, 4% SDS, 100 mM DTT [dithiotreitol], 0.02% bromophenol blue, 20% glycerin) was added to the proteins in a 1:3 ratio, and denatured at 100°C for 5 minutes. After cooling off on ice, this was quickly centrifuged and applied to the gel. 25 The same amount of protein was used for each track (35 µg total protein). The hydro-cooled gel run was done at room temperature and at a constant 50 V. Kaleidoscope Prestained Standard (BioRad) was used as the standard length.

30 Western blot and Immunodetection:

Transfer of the proteins from SDS-PAGE to a PVDF (polyvinyl difluoride) membrane (Hybond-P, Amersham) was done using a semidry method according to Kyhse-Anderson (J. Biochem. Biophys. Methods 10:203-210, 1984) at room temperature and a constant 0.5
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mA/cm² for 1.5 hours. A cathode buffer (30 mM tris, 40 mM glycine, 10% methanol, and 0.01% SDS, pH 9.4), anode buffer I (300 mM tris, pH 10.4, 10% methanol), and anode buffer II (30 mM tris, pH 10.4, 10% methanol) were used as the transfer buffers.

5 Before assembling the blot stack with 3MM Whatman paper (Schleicher & Schüll) the gel was incubated in cathode buffer, and the PVDF membrane (previously for 30 seconds in 100% methanol) in anode buffer II (5 minutes): 2 layers of 3MM paper (anode buffer I), 1 layer 3MM paper (anode buffer II), PVDF

10 membrane, gel, 3 layers 3MM paper (cathode buffer). To analyze electrophoretic transfer, both the post-blot gels and the blot membranes were stained after immunodetection using Coomassie (0.1% Coomassie G250, 45% methanol, 10% glacial acetic acid).

15 After transfer, the blot membrane was incubated in 1% skim milk powder/PBS/0.1% Tween-20 for one hour at room temperature. After that, it was washed three times for 3 minutes with 0.1% Tween-20/PBS. All subsequent antibody incubations and washings were done using 0.1% Tween-20/PBS. Incubation with the primary

20 antibody (human EGFR extracellular domain, specific goat IgG, Catalogue No. AF231, R&D Systems) was done on a shaker for two hours at room temperature at a concentration of 1.5 µg/ml. After that it was washed 3 x 5 minutes and incubated for one hour at room temperature with the secondary antibody (labeled donkey

25 anti-goat IgG horseradish peroxidase, Santa Cruz Biotechnology) at a dilution of 1:10,000. After washing (3 x 3 minutes in PBS/0.1% Tween-20) detection was immediately done by means of ECL reaction (enhanced chemoluminescence). To 18 ml of distilled water was pipetted 200 µl Solution A (250 mM luminol, Roth,

30 dissolved in DMSO), 89 µl Solution B (90 mM p-coumaric acid, Sigma, dissolved in DMSO), and 2 ml 30% H₂O₂ solution. Depending on membrane size, 4-6 ml was pipetted directly onto the membrane, incubated for 1 minute at room temperature, and then layed immediately on x-ray film (Biomax MS, Kodak).

The sequences used here are contained in Table 3 below, as well as in sequence protocols SQ153, 157, 158, 168-173.

ES-7	SQ168 SQ169	(A) 5'- AACACCGCAGCAUGUCAAGAU -3' (B) 3'- UUUUGUGGCGUCGUACAGUUC -5'	2-19-2
ES-8	SQ170 SQ171	(A) 5'- AAGUUAAAAUCCCGUCGCUAU -3' (B) 3'- CAAUUUUAAGGGCAGCGAUAGU -5'	2 ⁵ -19- 2 ⁵
ES2A/ ES5B	SQ172 SQ173	(A) 5'- AGUGUGAUCCAAGCUGUCCCAA -3' (B) 3'- UUUCACACUAGGUUCGACAGGGUU -5'	0-22-2
K2	SQ157 SQ158	(A) 5'- ACAGGAUGAGGAUCGUUUCGCAUG -3' (B) 3'- UCUGUCCUACUCCUAGCAAAGCGU -5'	2-22-2
K1A/ K2B	SQ153 SQ158	(A) 5'- ACAGGAUGAGGAUCGUUUCGCA -3' (B) 3'- UCUGUCCUACUCCUAGCAAAGCGU -5'	0-22-2

Table 3

Inhibition of EGFR expression in U-87 MG glioblastoma cells:

24 hours after seeding the cells, they were transfected with 10
nM dsRNA as noted (oligofectamine). After 72 hours, the cells
were harvested and the proteins isolated. Separation of the
proteins was done in 7.5% SDS-PAGE. 35 µg total protein was
applied to each track. The corresponding Western blot analysis
may be seen in Figure 24, which shows that with the specific
anti-EGFR-directed dsRNA with a 2nt overhang at the 3'-end of
the antisense strand, EGFR expression after transfection in U-87
MG cells is significantly inhibited in comparison to the
corresponding controls. This inhibition of expression of an
endogenous gene by means of specific dsRNA confirms the results
noted in Example II, of the inhibition of the expression of an

artificial gene inserted into the cell after transient transfection. The inhibition of EGFR expression mediated by ES-7 and ES-8 is notably smaller. The dsRNAs used in Figure 24 are shown in Table 3.

5

VI. Inhibiting expression of multi-drug resistance gene 1 (MDR1):

Test protocol:

- 10 In vitro detection of the blocking of MDR1 expression was done using the colon cancer cell line LS174T (ATCC - American Type Culture Collection; Tom et al., 1976). It is known of this cell line that expression of MDR1 is inducible by adding rifampicin to the culture medium (Geick et al., 2001). Transfection was
- 15 done using a variety of commercially available transfection kits (Lipofectamine, Oligofectamine, both from Invitrogen; TransMessenger, Qiagen), of which the TransMessenger kit proved to be the most suitable for this cell line.
- 20 Four short double-stranded ribonucleic acids (R1-R4) were used to conduct the RNA interference experiments. Their sequences are shown in Table 4. The ribonucleic acids are homologous with segments of the coding sequence of MDR1 (sequence protocol SQ 30). Sequences R1-R3 consist of a 22-mer sense strand and a 24-
- 25 mer antisense strand, whereby the resulting double strand exhibits a 2-nucleotide overhang at its 3'-end (0-22-2). Sequence R4 corresponds to R1; however it consists of a 19-mer double-stranded, each with 2-nucleotide overhangs at each 3'-end (2-19-2).

30

<u>Name</u>	<u>Sequence protocol No.</u>	<u>Sequence</u>	<u>Position in Data bank-# AF016535</u>
Seq	SQ141	5'- CCA UCU CGA AAA GAA GUU AAG A-3'	1320-1342
R1	SQ142	3'-UG GGU AGA GCU UUU CUU CAA UUC U-5'	1335-1318
Seq	SQ143	5'- UAU AGG UUC CAG GCU UGC UGU A-3'	2599-2621
R2	SQ152	3'-CG AUA UCC AAG GUC CGA ACG ACA U-5'	2621-2597
Seq	SQ144	5'- CCA GAG AAG GCC GCA CCU GCA U-3'	3778-3799
R3	SQ145	3'-UC GGU CUC UUC CGG CGU GGA CGU A-5'	3799-3776
Seq	SQ146	5'- CCA UCU CGA AAA GAA GUU AAG-3'	1320-1341
R4	SQ147	3'-UG GGU AGA GCU UUU CUU CAA U -5'	1339-1318
			<u>Position in Data bank-# AF402779</u>
K1A/	SQ153	5'- ACA GGA UGA GGA UCG UUU CGC A-3'	2829-2808
K2B	SQ158	3'-UC UGU CCU ACU CCU AGC AAA GCG U-5'	2808-2831

Table 4

- 5 The sequences shown in Table 4 are designated as sequences SQ141-147, 152, 153, and 158 in the sequence protocol. The dsRNA was in each case transfected into the cells as double assays at a concentration of 175 nM, which had on the day before been seeded in 12-well plates at 3.8×10^5 cells/well. For each
- 10 transfection assay, 93.3 μ l EC-R buffer (TransMessenger kits, Qiagen, Hilden) was mixed with 3.2 μ l Enhancer R, and then 3.5 μ l of the particular 20 μ M dsRNA was added, mixed well, and incubated for 5 minutes at room temperature. After the addition of 6 μ l TransMessenger transfection reagent, the transfection

assay was mixed vigorously for 10 seconds, and then incubated for 10 minutes at room temperature. In the meantime, the medium was extracted from the cells, washed once with PBS (phosphate-buffered saline), and then 200 μ l fresh medium without FCS was added to the cells in each well. After 10-minute incubation, 100 μ l FCS-free medium was pipetted into each transfection assay, mixed, and the mixture was then pipetted drop by drop onto the cells (the dsRNA concentration of 175 μ M relates to 400 μ l medium total volume). The dsRNA/TransMessenger complexes were incubated with the cells for 4 hours at 37°C in FCS-free medium. The medium was then changed; the fresh medium contained 10 μ M rifampin and 10% FCS. A non-specific dsRNA sequence that exhibits no homologies with the MDR1 gene sequence was used (K) as a control, and a MOCK transfection was conducted that contained all reagents except for dsRNA.

The cells were harvested after 24, 48, and 72 hours, and total RNA was extracted with the RNeasy mini kit from Qiagen. 10 μ g total protein from each sample was then separated by electrophoresis on a 1% agarose-formaldehyde gel, blotted on a nylon membrane, and then hybridized as an internal control with specific probes that had been random-marked with 5'- α^{32} P-dCTP, first against MDR1, and after the blot had been stripped, against GAPDH, and then exposed on x-ray film.

The x-ray film was digitized (Image Master, VDS, Pharmacia) and quantified using Image-Quant software. At that time, adjustment between the MDR1-specific bands and the corresponding GAPDH bands was done.

Results:

Figs. 25 and 26 show Northern blots (Figs. 26a, 26a) with quantitative analysis of the MDR1-specific bands after adjustment with the corresponding GAPDH values (Figs. 25b, 26p).

A reduction in the MDR1-mRNA by as much as 55% was observed in comparison to the MOCK transfection, and by as much as 45% in comparison to the non-specific control transfection. After 48 hours there was a significant reduction in the MDR1-mRNA level in the dsRNA constructs designated as R1, R2, and R3 (Table 4). With the R4 dsRNA constructs, no significant reduction in comparison to the controls was observed after 48 hours (Figs. 26a and 26b). After 74 hours, there was a markedly stronger reduction in the MDR1-mRNA level with R1, R2, and R3 with the controls in comparison to the values at 48 hours (Figs. 25a and 26b). A significant decrease in the MDR1-mRNA level was seen at this time with R4 as well. Thus, the constructs with a 2nt. overhang at the 3'-end of the antisense strand and a double-stranded region consisting of 22 nucleotide pairs reduces the MDR1-mRNA level more efficiently than do constructs with 2nt overhangs at the 3'-end of both strands (antisense strand and sent strand) and a double-stranded region consisting of 19 nucleotide pairs, relatively independent of the sequence region homologous to the MDR1 gene in each case (after 48 hours; Figure 26b). The results strengthen the findings in Example IV, which describe the inhibition of EGFR gene expression by means of specific dsRNAs after transfection in U-87 MG cells.

Transfection efficiency was determined in a separate experiment with the help of a DNA oligonucleotide marked with Texas red (TexRed-A[GATC]₅T; also transfected with 175 nM) (Figs. 27a, 27b; 400x enlargement, 48 hours after transfection). Transfection efficiency was approximately 50% on the basis of red fluorescent cells in comparison to total cell number. If one takes the transfection rate of cells of approximately 50% into consideration, then it seems reasonable to conclude that given the observed decrease in the MDR1-mRNA level by approximately 45-55% (compared with the controls), that MDR1-mRNA was almost

completely and specifically broken down in all cells that were successfully transfected with specific dsRNA.

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122

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125

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126

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128

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129

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135

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   tgggcatcgg cacagtccctg gaccaagcgg agacggctgg agcgcgactc gtcgtgctcg 960
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   tgtccagcac tggagaaatc ccccttttatg gcaaagccat ccccatcgag accatcaagg 1080
   gggggaggca cctcatttct tgccattcca agaagaaatg tgatgagctc gccgcgaagc 1140
   tgtccggcct cggactcaat gctgtagcat attaccgggg ccttgatgta tccgtcatac 1200
   caactagcgg agacgtcatt gtcgtagcaa cggacgctct aatgacgggc tttaccggcg 1260
25  atttcgactc agtgcacgac tgcaatacat gtgtcaccca gacagtgcac ttcagcctgg 1320
   acccgacctt caccattgag acgacgaccg tgccacaaga cgcggtgtca cgctcgagc 1380
   ggcgaggcag gactggtagg ggcaggatgg gcatttacag gtttgtgact ccaggagaac 1440
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   ggtacgagct cagccccgcc gagacctcag ttaggttgcg ggcttaccta aacacaccag 1560
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   acatagacgc ccatttcttg tcccagacta agcaggcagg agacaacttc ccctacctgg 1680
   tagcatacca ggctacgggtg tgcgccaggc ctacagctcc acctccatcg tgggaccaa 1740
   tgtggaagtg tctcatagcg ctaaagccta cgctgcacgg gccaacgccc ctgctgtata 1800
   ggctgggagc cgttcaaaac gaggttacta ccacacaccc cataaccaa 1860
35  catgcatgct ggctgacctg gaggtcgta cg 1892

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<210> 134

<211> 822

40 <212> DNA

<213> Homo sapiens

<300>

<302> stmn cell factor

45 <310> M59964

<400> 134

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   actaaattgg tggcaaatct tccaaaagac tacatgataa ccctcaaata tgtccccggg 180
   atggatgttt tgccaagtca ttgttgagata agcgagatgg tagtacaatt gtcagacagc 240
   ttgactgata ttctggacaa gttttcaaat atttctgaag gcttgagtaa ttattccatc 300
   atagacaaac ttgtgaatat agtcgatgac cttgtggagt gcgtcaaaga aaactcatct 360
   aaggatctaa aaaaatcatt caagagccca gaaccaggc tctttactcc tgaagaattc 420
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   agtgattgtg tggtttcttc aacattaagt cctgagaaag attccagagt cagtgtcaca 540
   aaaccattta tgttaccccc tgttgacgac agctccctta ggaatgacag cagtagcagt 600
   aataggaagg ccaaaaatcc cctgggagac tccagcctac actgggcagc catggcattg 660
   ccagcattgt tttctcttat aattggcttt gcttttgag ccttatactg gaagaagaga 720
60  cagccaagtc ttacaagggc agttgaaaat atacaaatta atgaagagga taatgagata 780

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137

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822

5 <210> 135
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 <213> Homo sapiens

10 <300>
 <302> TGFalpha
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<400> 135
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 gtgtcccatt ttaatgactg cccagattcc cacactcagt tctgcttcca tggaaacctgc 180
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 cgctgtgagc atgcggacct cctggccgtg gtggctgccca gccagaagaa gcaggccatc 300
 accgccttgg tgggtggtctc catcgtggcc ctggctgtcc ttatcatcac atgtgtgtctg 360
 20 atacactgct gccaggtccg aaaacactgt gagtgtgtgcc gggccctcat ctgccggcac 420
 gagaagccca gcgcctcct gaagggaaga accgcttgct gccactcaga aacagtgggtc 480
 tga 483

25 <210> 136
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 <213> Homo sapiens

30 <300>
 <302> GD3 synthase
 <310> NM003034

<400> 136
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 40 atggggaaga gcatgtggtg tgacggggag tttttatact cattcaccat tgacaattca 360
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 45 tgggtccagaa agacatttgc ggacaacatg aaaatctata accacagtta catctacatg 660
 cctgcctttt ctatgaagac aggaacagag ccactcttga gggtttatta tacactgtca 720
 gatgttgggt ccaatcaaac agtgctgttt gccaaaccca actttctgcg tagcattgga 780
 aagttctgga aaagtagagg aatccatgcc aagcgcctgt ccacaggact ttttctgggtg 840
 agcgcagctc tgggtctctg tgaagagggt gccatctatg gcttctggcc cttctctgtg 900
 50 aatatgcagc agcagcccat cagccaccac tactatgaca acgtcttacc cttttctggc 960
 ttccatgccca tgcccaggga atttctccaa ctctggtatc ttcataaaaat cggtgcactg 1020
 agaatgcagc tggacctatg tgaagatacc tcaactccagc ccacttccta g 1071

55 <210> 137
 <211> 744
 <212> DNA
 <213> Homo sapiens

60 <300>

138

<302> PGF14

<310> NM004115

<400> 137

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   aacggcaacc tgggtggatat cttctccaaa gtgcgcatct tcggcctcaa gaagcgagg 180
   ttgcggcgcc aagatcccca gctcaagggt atagtacca ggttatattg caggcaaggc 240
   tactacttgc aaatgcaccc cgatggagct ctcgatggaa ccaaggatga cagcactaat 300
10 tctacactct tcaacctcat accagtggga ctacgtgttg ttgccatcca gggagtga 360
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   cctgaatgca agtttaaaaga atctgttttt gaaaattatt atgtaattcta ctcatccatg 480
   ttgtacagac aacaggaaatc tggtagagcc tggtttttgg gattaaataa ggaagggcaa 540
   gctatgaaag ggaacagagt aaagaaaacc aaaccagcag ctcattttct acccaagcca 600
15 ttggaagtgt ccatgtaccg agaaccatct ttgcatgatg ttggggaaac ggtcccgaag 660
   cctggggtga cgccaagtaa aagcacaagt gcgtctgcaa taatgaatgg aggcaaacca 720
   gtcaacaaga gtaagacaac atag                                     744

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20 <210> 138

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<212> DNA

<213> Human immunodeficiency virus

25 <300>

<302> gag (HIV)

<310> NC001802

<400> 138

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   ctagaacgat tcgcagttaa tcctggcctg ttagaacatg cagaaggctg tagacaaata 180
   ctgggacagc tacaaccatc ccttcagaca ggatcagaag aacttagatc attatataat 240
   acagtagcaa cctctattg tgtgcatcaa aggatagaga taaaagacac caaggaagct 300
35 ttagacaaga tagaggaaga gcaaaacaaa agtaagaaa aagcacagca agcagcagct 360
   gacacaggac acagcaatca ggtcagccaa aattacccta tagtcagaa catccagggg 420
   caaatggtac atcaggccat atcacctaga actttaaatg catgggtaaa agtagtagaa 480
   gagaaggctt tcagcccaga agtgataccc atgttttcag cattatcaga aggagccacc 540
   ccacaagatt taaacaccat gctaaacaca gtggggggac atcaagcagc catgcaaatg 600
40 ttaaaagaga ccatcaatga ggaagctgca gaatgggata gagtgcattc agtgcattgc 660
   gggcctattg caccaggcca gatgagagaa ccaaggggaa gtgacatagc aggaactact 720
   agtacccttc aggaacaaat aggatggatg acaataatc cacctatccc agtaggagaa 780
   atttataaaa gatggataat cctgggatta aataaaatag taagaatgta tagccctacc 840
   agcattcttg acataagaca aggaccaaa gaaaccctta gagactatgt agaccggttc 900
45 tataaaactc taagagccga gcaagcttca caggaggtaa aaaattggat gacagaaacc 960
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   gctacactag aagaaatgat gacagcatgt caggagtagt gaggaccggg ccataaggca 1080
   agagtttttg ctgaagcaat gagccaagta acaaattcag ctaccataat gatgcagaga 1140
   ggcaatttta ggaaccaaag aaagattgtt aagtgtttca attgtggcaa agaagggcac 1200
50 acagccagaa attgcagggc ccttaggaaa aagggtgtgt ggaaatgtgg aaaggaagga 1260
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   tacaagggaa ggccagggaa ttttcttcag agcagaccag agccaacagc cccaccagaa 1380
   gagagcttca ggtctgggtg agagacaaca actccccctc agaagcagga gccgatagac 1440
   aaggaactgt atcctttaac ttccctcagg tcactctttg gcaacgaccc ctctgcacaa 1500
55 taa                                     1503

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<210> 139

<211> 1101

60 <212> DNA

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139

<213> Human immunodeficiency virus

<300>

<302> TARBP2

5 <310> NM004178

<400> 139

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10 agaataggga agacgcctgt gtacgacctt ctcaaagccg agggccaagc ccaccagcct 180
aatttcacct tccgggtcac cgttggcgac accagctgca ctggtcaggg cccagcaag 240
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gacattccgg tttttactgc tgcagcagct gctaccccag ttccatctgt agtcctaacc 420
15 aggagccccc ccatggaact gcagccccct gtctcccctc agcagtctga gtgcaacccc 480
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ttcattgaga ttgggagtg cacttccaaa aaattggcaa agcggaatgc ggcgccaaa 660
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ggactctgcc agtgccctgt ggaactgtcc acccagccgg ccactgtgtg tcatggctct 1020
25 gcaaccacca gggaggcagc ccgtggtgag gctgcccgcc gtgccctgca gtacctcaag 1080
atcatggcag gcagcaagtg a 1101

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<210> 140

30 <211> 219

<212> DNA

<213> Human immunodeficiency virus

<300>

35 <302> TAT (HIV)

<310> U44023

<400> 140

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40 gcttgtagca cttgtattg taaagagtgt tgctttcatt gccagtttg tttcataaca 120
aaaggcttag gcatctccta tggcaggaag aagcggagac agcgacgaag aactcctcaa 180
ggtcatcaga ctaatcaagt ttctctatca aagcagtaa 219

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45 <210> 141

<211> 22

<212> RNA

<213> Synthetic sequence

50 <220>

<223> Description of the synthetic sequence: sense strand
(R1A) of a dsRNA that is homologous to an MDR1 sequence

<400> 141

55 ccaucucgaa aagaaguuaa ga

22

<210> 142

<211> 24

60 <212> RNA

140

<213> Synthetic sequence
 <220>
 <223> Description of the synthetic sequence:
 5 antisense strand (R1B) of a dsRNA, that it
 complementary to an MDR1 sequence
 <400> 142
 10 ucuaacuuc uuuucgagau gggg 24
 <210> 143
 <211> 22
 <212> RNA
 15 <213> Synthetic sequence
 <220>
 <223> Description of the synthetic sequence: sense strand
 (R2A) of a dsRNA that is homologous to an MDR1 sequence
 20 <400> 143
 uauagguucc aggcugcug ua 22
 <210> 144
 <211> 22
 <212> RNA
 25 <213> Synthetic sequence
 <220>
 <223> Description of the synthetic sequence: sense strand
 (R3A) of a dsRNA that is homologous to an MDR1 sequence
 30 <400> 144
 35 ccagagaagg ccgcaccugc au 22
 <210> 145
 <211> 24
 40 <212> RNA
 <213> Synthetic sequence
 <220>
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 45 antisense strand (R3B) of a dsRNA, that it
 complementary to an MDR1 sequence
 <400> 145
 50 augcaggugc ggccuucucu ggcu 24
 <210> 146
 <211> 21
 <212> RNA
 55 <213> Synthetic sequence
 <220>
 <223> Description of the synthetic sequence: sense strand
 (R4A) of a dsRNA that is homologous to an MDR1 sequence
 60

141

- <400> 146
ccaucucgaa agaaguuaa g 21
- 5 <210> 147
<211> 21
<212> RNA
<213> Synthetic sequence
- 10 <220>
<223> Description of the synthetic sequence:
antisense strand (R4B) of a dsRNA, that it
complementary to an MDR1 sequence
- 15 <400> 147
uaacuucuuu ucgagauggg u 21
- 20 <210> 148
<211> 22
<212> RNA
<213> Synthetic sequence
- 25 <220>
<223> Description of the synthetic sequence: sense strand
(S1A) of a dsRNA, that is homologous to the YFP- and
GFP sequence, respectively
- 30 <400> 148
ccacaugaag cagcacgacu uc 22
- 35 <210> 149
<211> 22
<212> RNA
<213> Synthetic sequence
- 40 <220>
<223> Description of the synthetic sequence:
antisense strand(S1B) of a dsRNA that is
complementary to the YFP- and GFP sequence, respectively
- 45 <400> 149
gaagucgugc ugcuucaugu gg 22
- 50 <210> 150
<211> 21
<212> RNA
<213> Synthetic sequence
- 55 <220>
<223> Description of the synthetic sequence:
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to the YFP- and GFP sequence, respectively
- 60 <400> 150
ccacaugaag cagcacgacu u 21

142

5 <210> 151
 <211> 21
 <212> RNA
 <213> Synthetic sequence
 <220>
 <223> Description of the synthetic sequence:
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 complementary to the YFP- and GFP sequence, respectively
 10 <400> 151
 gucgugcugc uucauguggu c 21
 15 <210> 152
 <211> 24
 <212> RNA
 <213> Synthetic sequence
 20 <220>
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 uacagcaagc cuggaaccua uagc 24
 30 <210> 153
 <211> 22
 <212> RNA
 <213> Synthetic sequence
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 35 <223> Description of the synthetic sequence: sense strand
 (K1A) of a dsRNA that is homologous to the 5'-UTR of
 the neomycin sequence
 <400> 153
 40 acaggagag gaucguuucg ca 22
 <210> 154
 <211> 22
 45 <212> RNA
 <213> Synthetic sequence
 <220>
 <223> Description of the synthetic sequence:
 50 antisense strand(K1B) of a dsRNA that is
 complementary to the 5'-UTR of the neomycin sequence
 <400> 154
 55 ugcgaaaacga uccucauccu gu 22
 <210> 155
 <211> 21
 <212> RNA
 60 <213> Synthetic sequence

<220>
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 (K3A) of a dsRNA that is homologous to the 5'-UTR of the
 5 neomycin sequence

 <400> 155
 gaugaggau c guuucgcaug a 21

 10 <210> 156
 <211> 21
 <212> RNA
 <213> Synthetic sequence

 15 <220>
 <223> Description of the synthetic sequence:
 antisense strand(K3B) of a dsRNA that
 20 complementary to the 5'-UTR of the neomycin sequence

 <400> 156
 augcgaaacg auccucaucc u 21

 25 <210> 157
 <211> 24
 <212> RNA
 <213> Synthetic sequence

 30 <220>
 <223> Description of the synthetic sequence: sense strand
 (K2A) of a dsRNA that is homologous to the 5'-UTR of the
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 35 <400> 157
 acaggaugag gaucguuucg caug 24

 40 <210> 158
 <211> 24
 <212> RNA
 <213> Synthetic sequence

 45 <220>
 <223> Description of the synthetic sequence:
 antisense strand(K2B) of a dsRNA that is
 complementary to the 5'-UTR of the neomycin sequence

 50 <400> 158
 ugcgaaacga uccucauccu gucu 24

 55 <210> 159
 <211> 24
 <212> RNA
 <213> Synthetic sequence

 60 <220>
 <223> Description of the synthetic sequence:
 antisense strand(S4B) of a dsRNA that is

complementary to the YFP- and GFP sequence, respectively

5 <400> 159
gaagucgugc ugcucaugu gguc 24

10 <210> 160
<211> 24
<212> RNA
<213> Synthetic sequence

15 <220>
<223> Description of the synthetic sequence: sense strand
(PKC1 A) of a dsRNA that is homologous to the
proteinkinase C sequence

20 <400> 160
cuucuccgcc ucacaccgcg gcaa 24

25 <210> 161
<211> 22
<212> RNA
<213> Synthetic sequence

30 <220>
<223> Description of the synthetic sequence:
antisense strand(PKC2 B) of a dsRNA that is
complementary to the proteinkinase C sequence

35 <400> 161
gcagcggugu gaggcggaga ag 22

40 <210> 162
<211> 21
<212> RNA
<213> Synthetic sequence

45 <220>
<223> Description of the synthetic sequence:
antisense strand(S12B) of a dsRNA that is
complementary to the YFP- and GFP sequence, respectively

50 <400> 162
aagucgugcu gcucaugug g 21

55 <210> 163
<211> 23
<212> RNA
<213> Synthetic sequence

60 <220>
<223> Description of the synthetic sequence:
antisense strand(S11B) of a dsRNA that is
complementary to the YFP- and GFP sequence, respectively

60 <400> 163
aagucgugcu gcucaugug guc 23

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	<211> 20	
5	<212> RNA	
	<213> Synthetic sequence	
	<220>	
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	<210> 165	
	<211> 22	
	<212> RNA	
20	<213> Synthetic sequence	
	<220>	
	<223> Description of the synthetic sequence: antisense strand(S13B) of a dsRNA that is complementary to the YFP- and GFP sequence, respectively	
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30	<210> 166	
	<211> 20	
	<212> RNA	
35	<213> Synthetic sequence	
	<220>	
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45	<210> 167	
	<211> 24	
	<212> RNA	
	<213> Synthetic sequence	
50	<220>	
	<223> Description of the synthetic sequence: sense strand (S4A) of a dsRNA that is homologous to the YFP- and GFP sequence, respectively	
55	<400> 167	
	ccacaugaag cagcacgacu ucuu	24
	<210> 168	
60	<211> 21	

<212> RNA
 <213> Synthetic sequence

 <220>
 5 <223> Description of the synthetic sequence: sense strand
 (ES-7A) of a dsRNA that is homologous to the human
 EGFR sequence

 <400> 168
 10 aacaccgcag caugucaaga u 21

 <210> 169
 <211> 21
 15 <212> RNA
 <213> Synthetic sequence

 <220>
 20 <223> Description of the synthetic sequence:
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 complementary to the human EGFR sequence

 <400> 169
 25 cuugacaugc ugccgguguuu u 21

 <210> 170
 <211> 22
 30 <212> RNA
 <213> Synthetic sequence

 <220>
 35 <223> Description of the synthetic sequence: sense strand
 (ES-8A) of a dsRNA that is homologous to the human
 EGFR sequence

 <400> 170
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 40 <210> 171
 <211> 22
 <212> RNA
 45 <213> Synthetic sequence

 <220>
 50 <223> Description of the synthetic sequence:
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 complementary to the human EGFR sequence

 <400> 171
 ugauagcgac gggaaauuuu ac 22

 55 <210> 172
 <211> 22
 <212> RNA
 <213> Synthetic sequence

 60 <220>

147

<223> Description of the synthetic sequence: sense strand
(ES-2A) of a dsRNA that is homologous to the human
EGFR sequence

5 <400> 172
agugugaucc aagcuguccc aa

22

10 <210> 173
<211> 24
<212> RNA
<213> Synthetic sequence

15 <220>
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complementary to the human EGFR sequence

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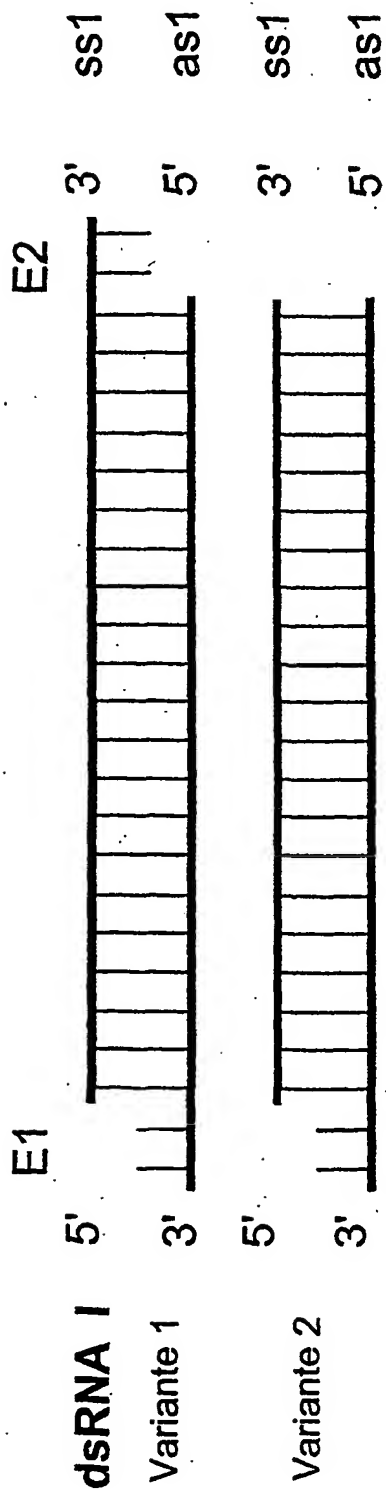


Fig. 1a

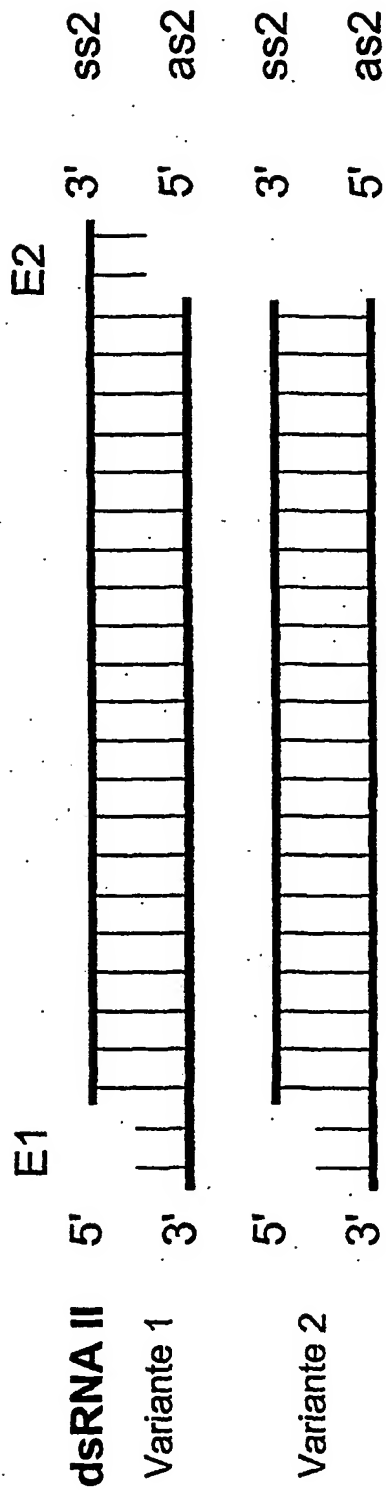


Fig. 1b

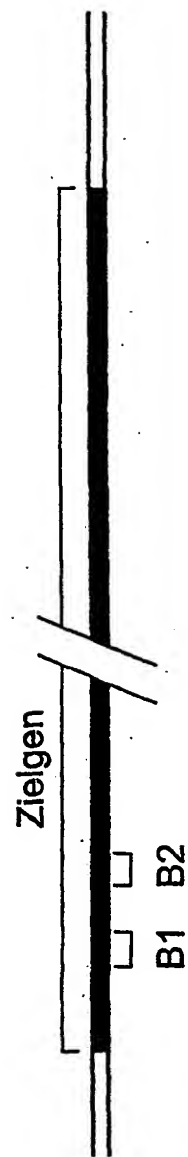


Fig. 2

2/20

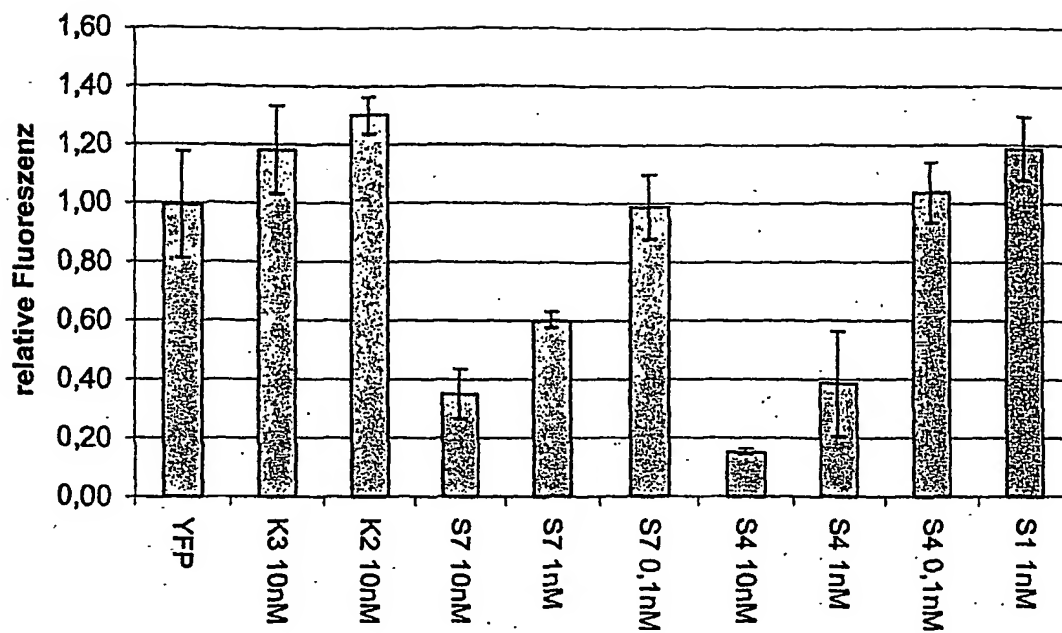


Fig. 3

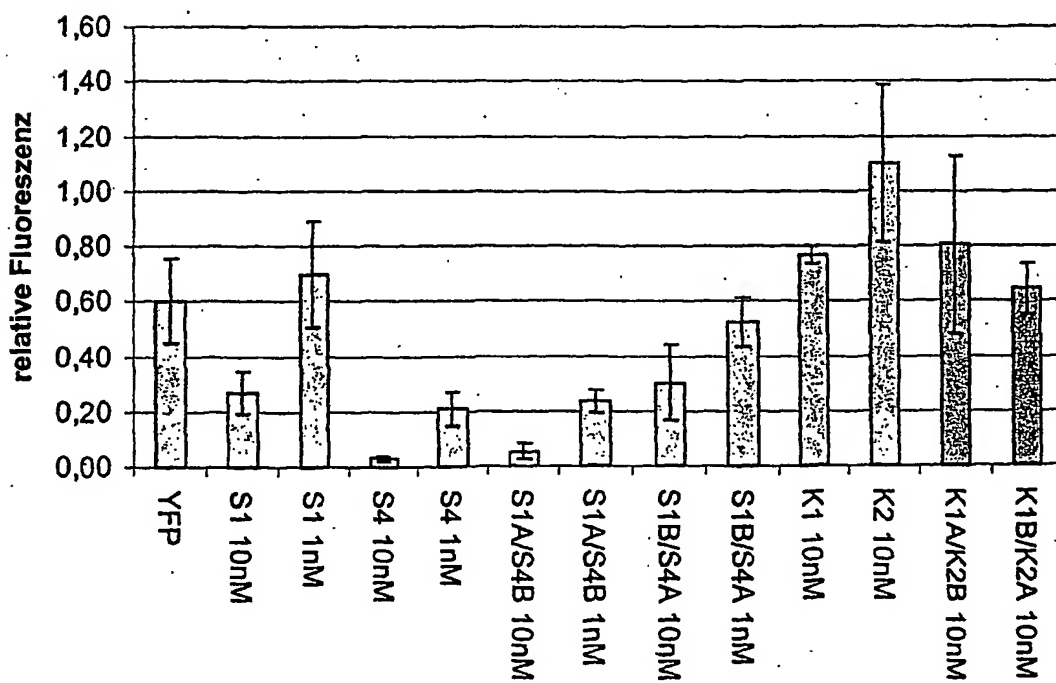


Fig. 4

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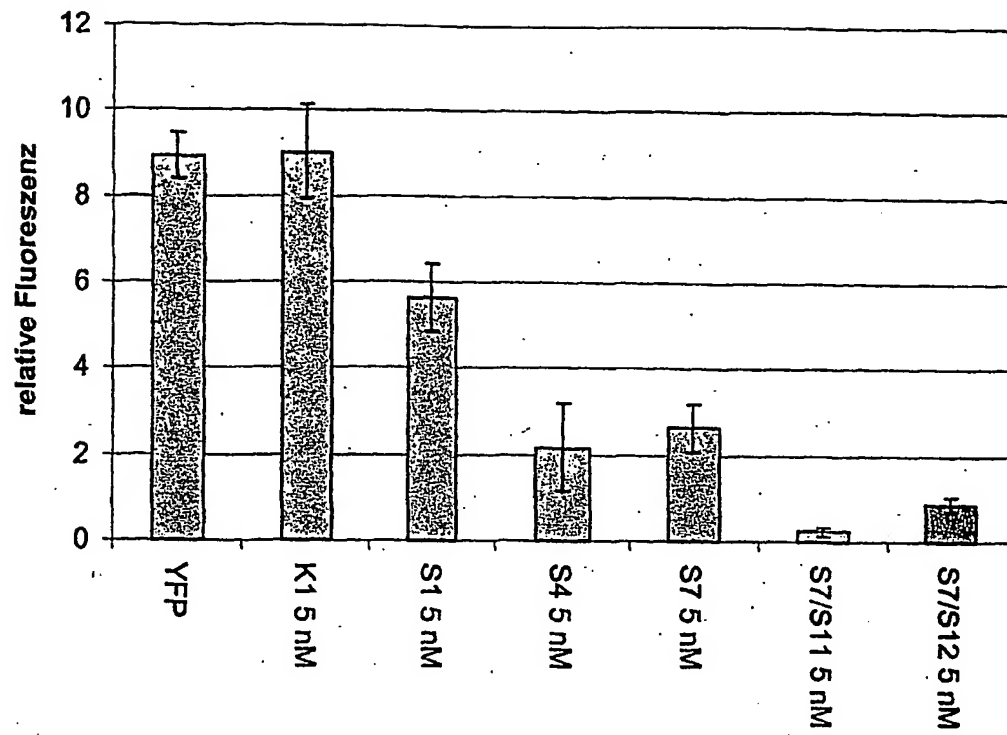


Fig. 5

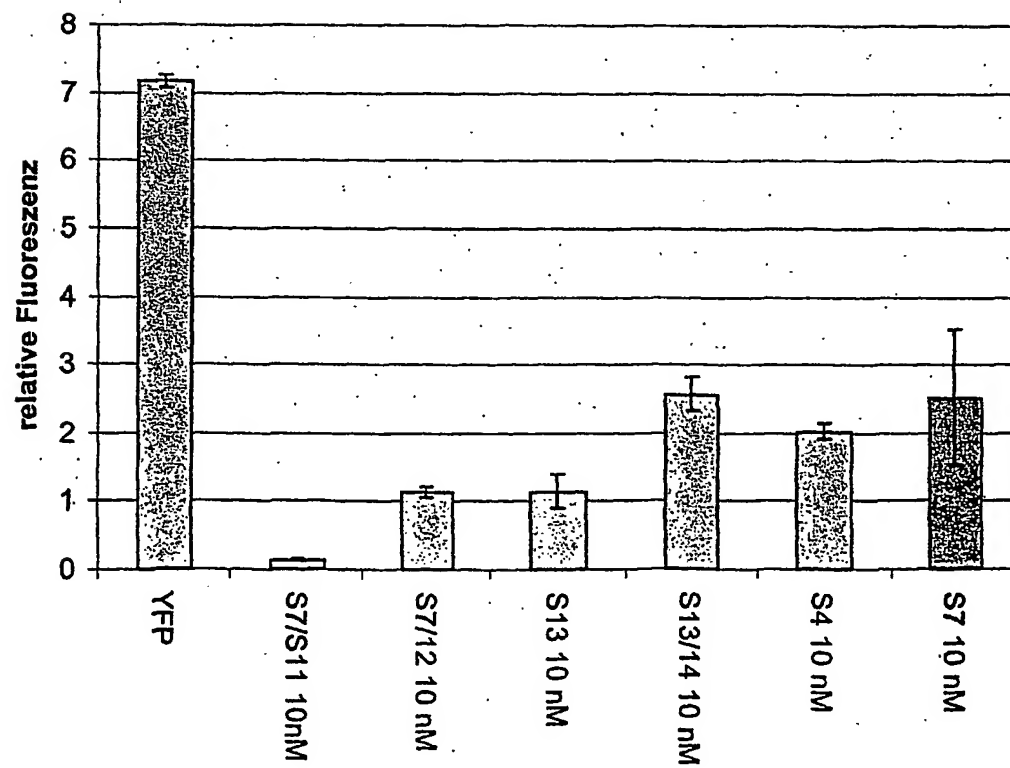


Fig. 6

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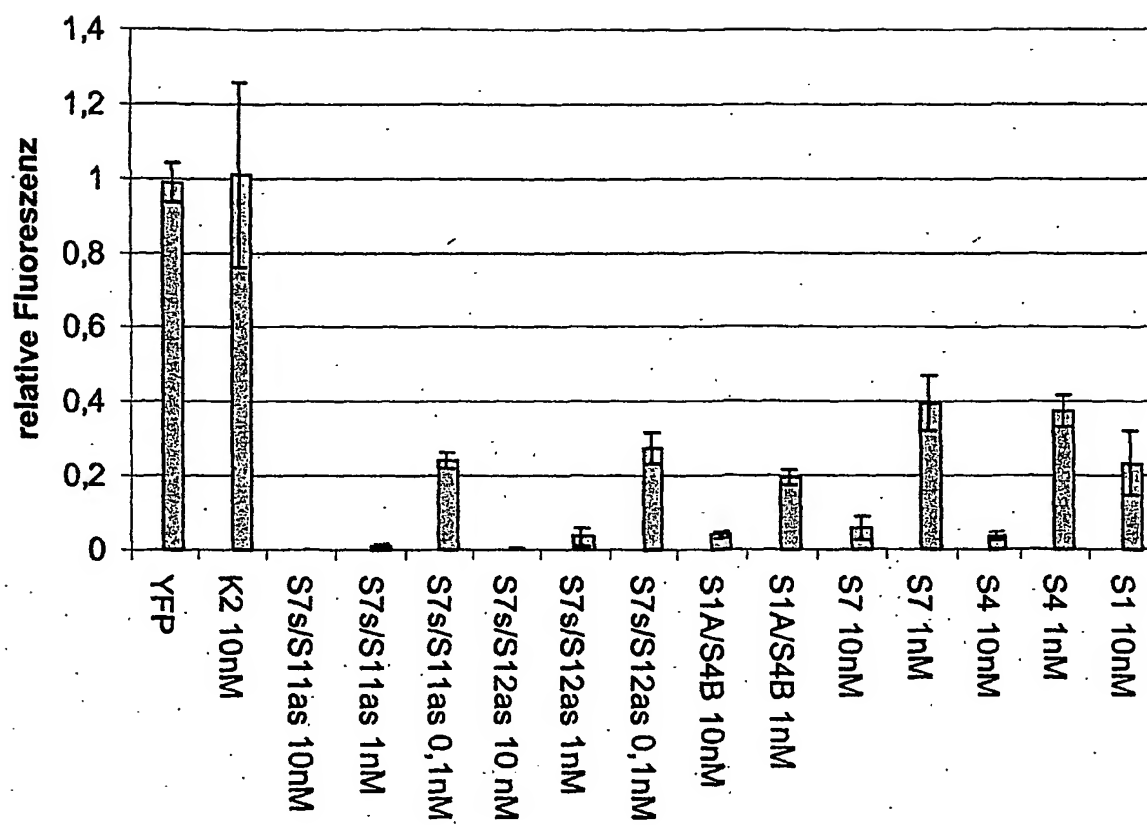


Fig. 7

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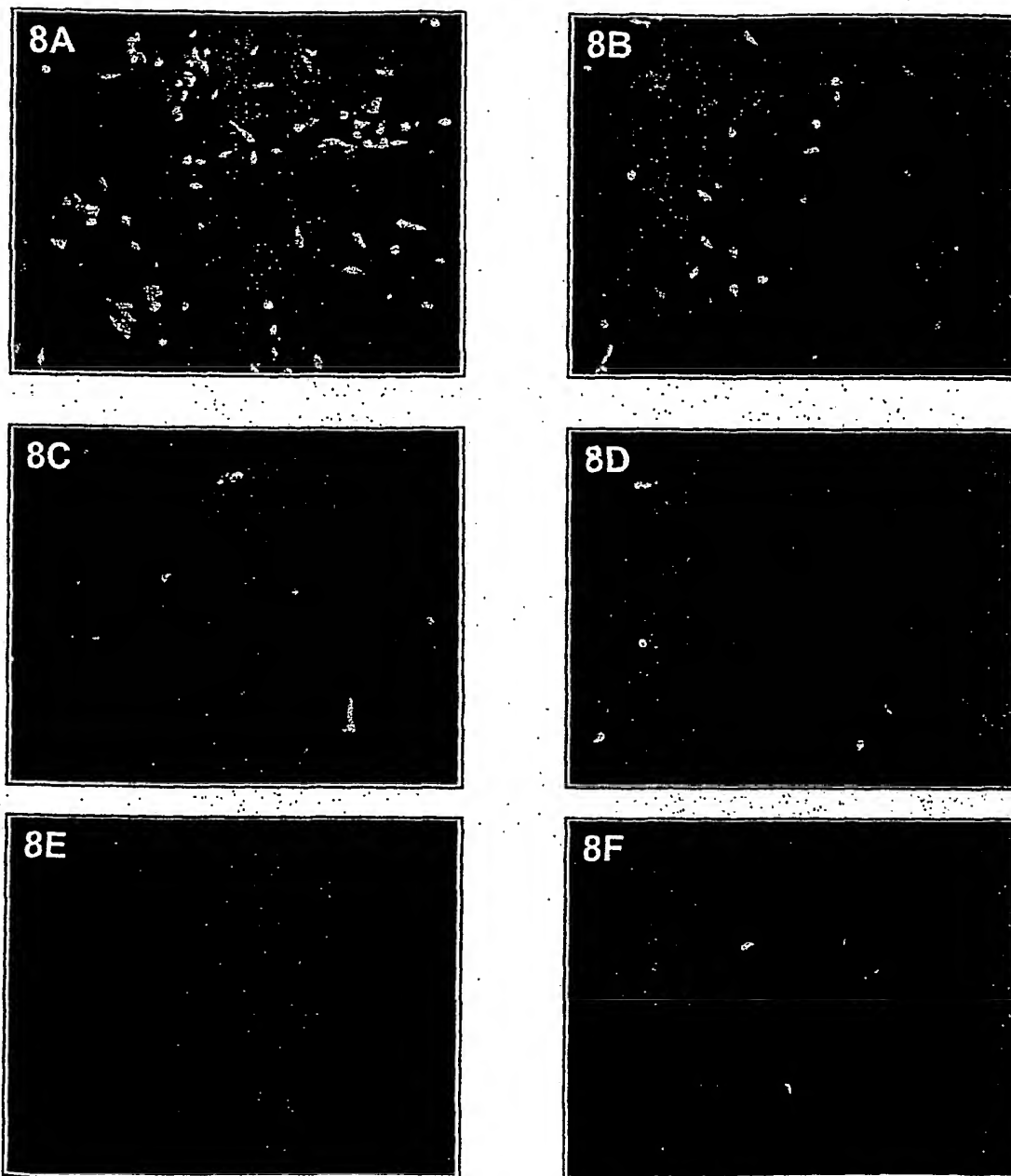


Fig. 8

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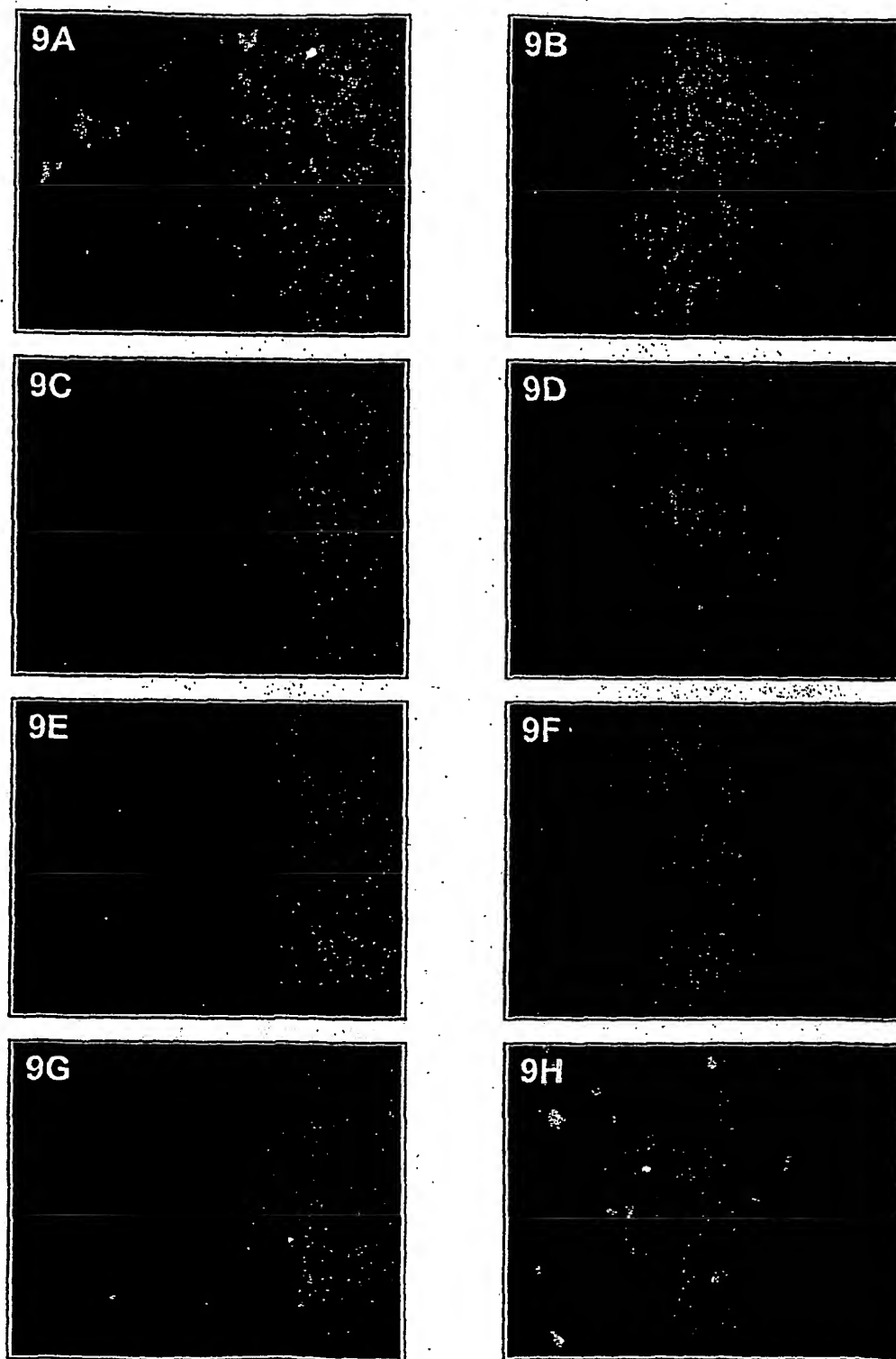


Fig. 9

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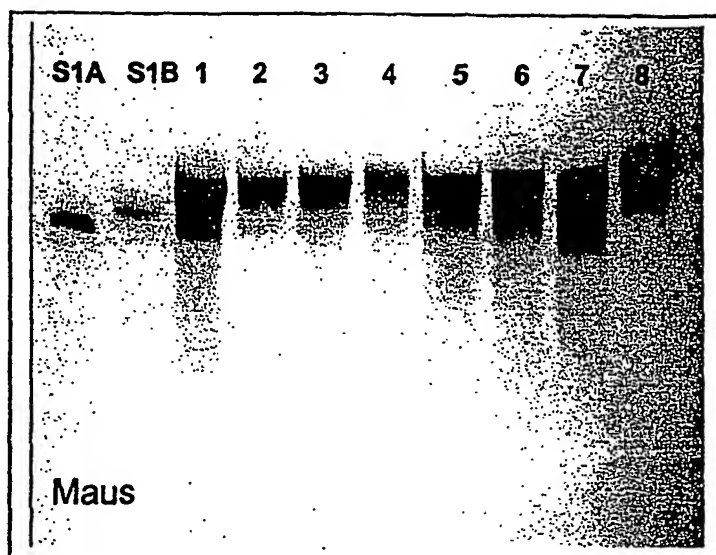


Fig. 10

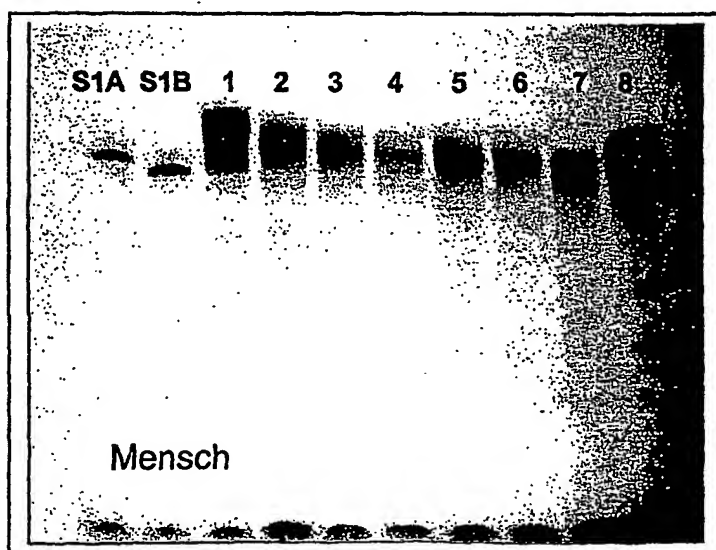


Fig. 11

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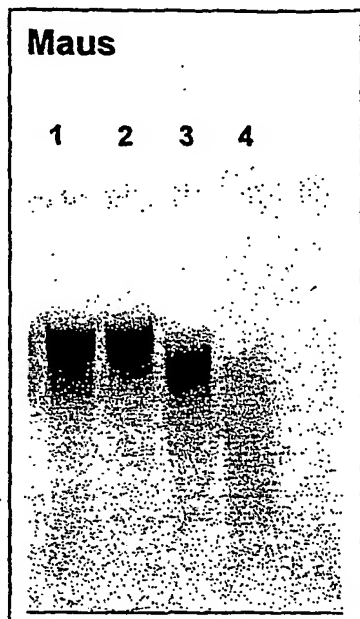


Fig. 12

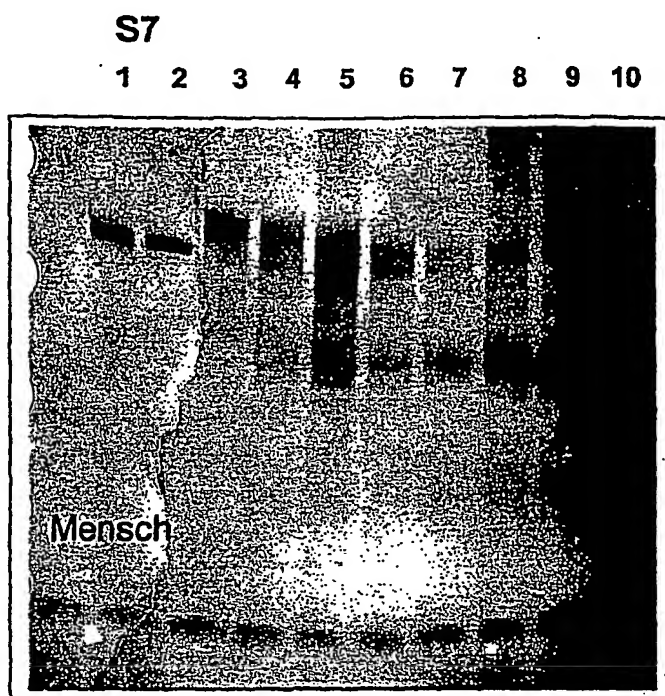


Fig. 13

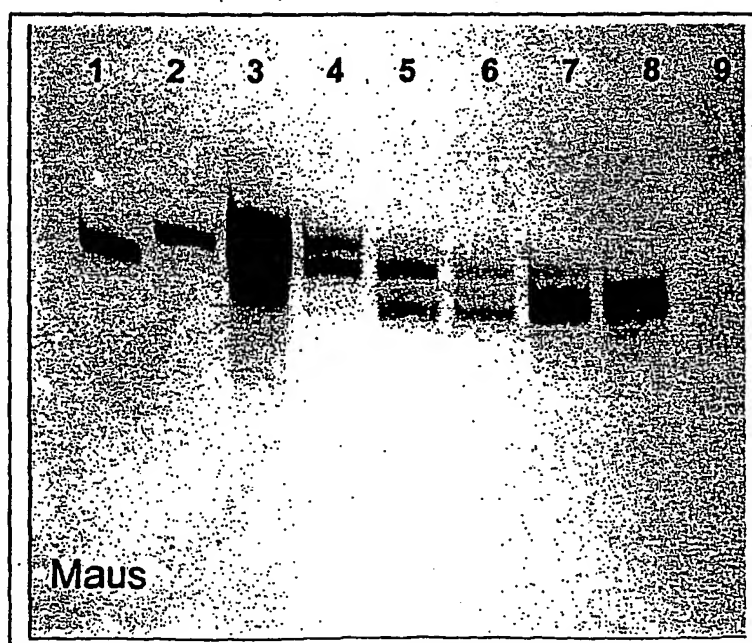


Fig. 14

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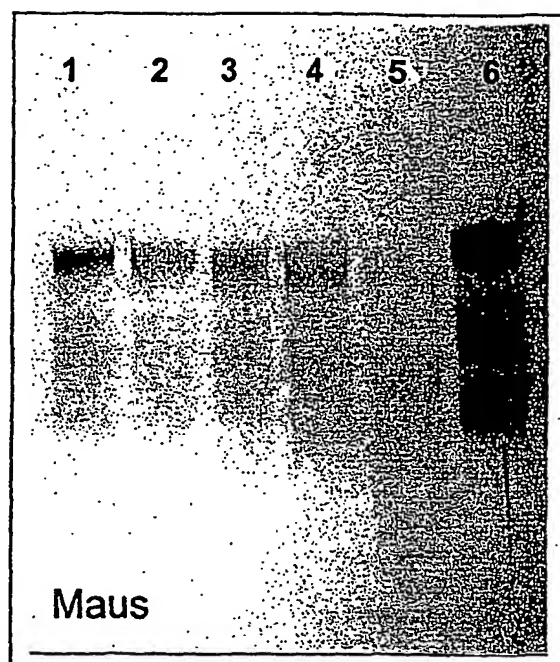


Fig. 15

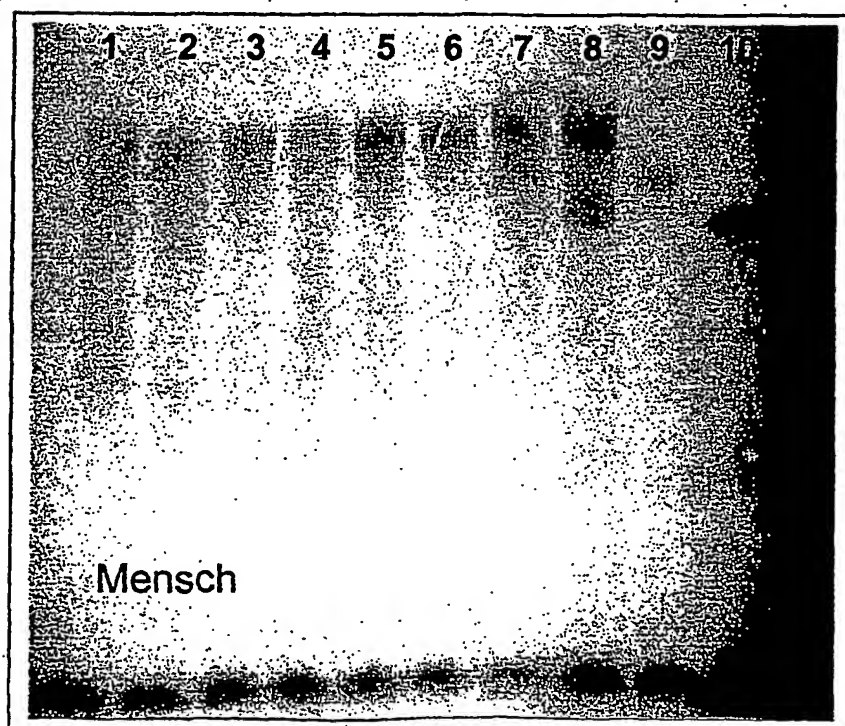


Fig. 16

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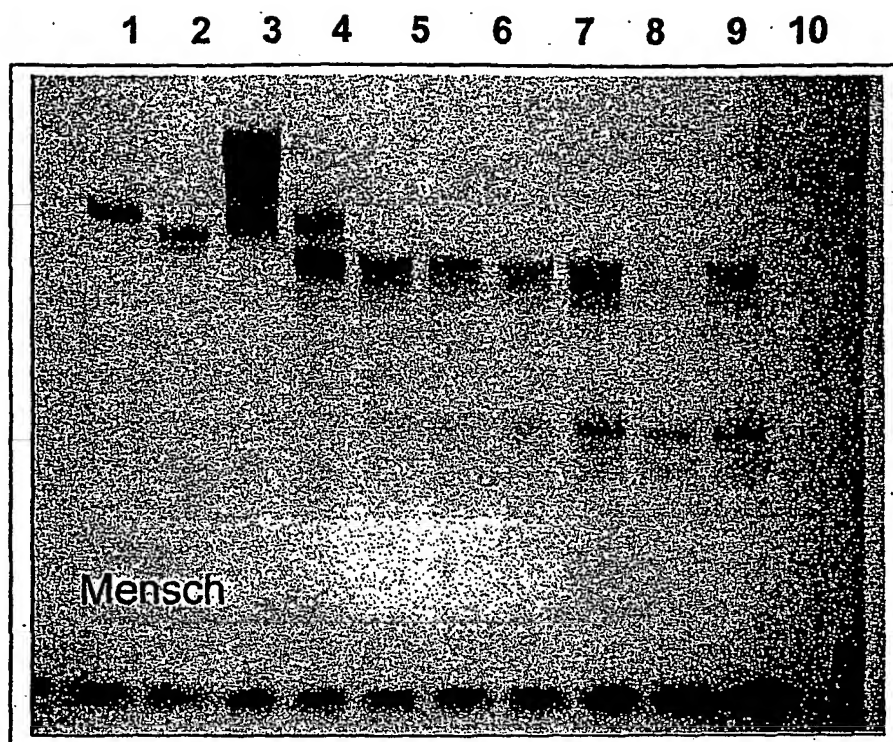


Fig. 17

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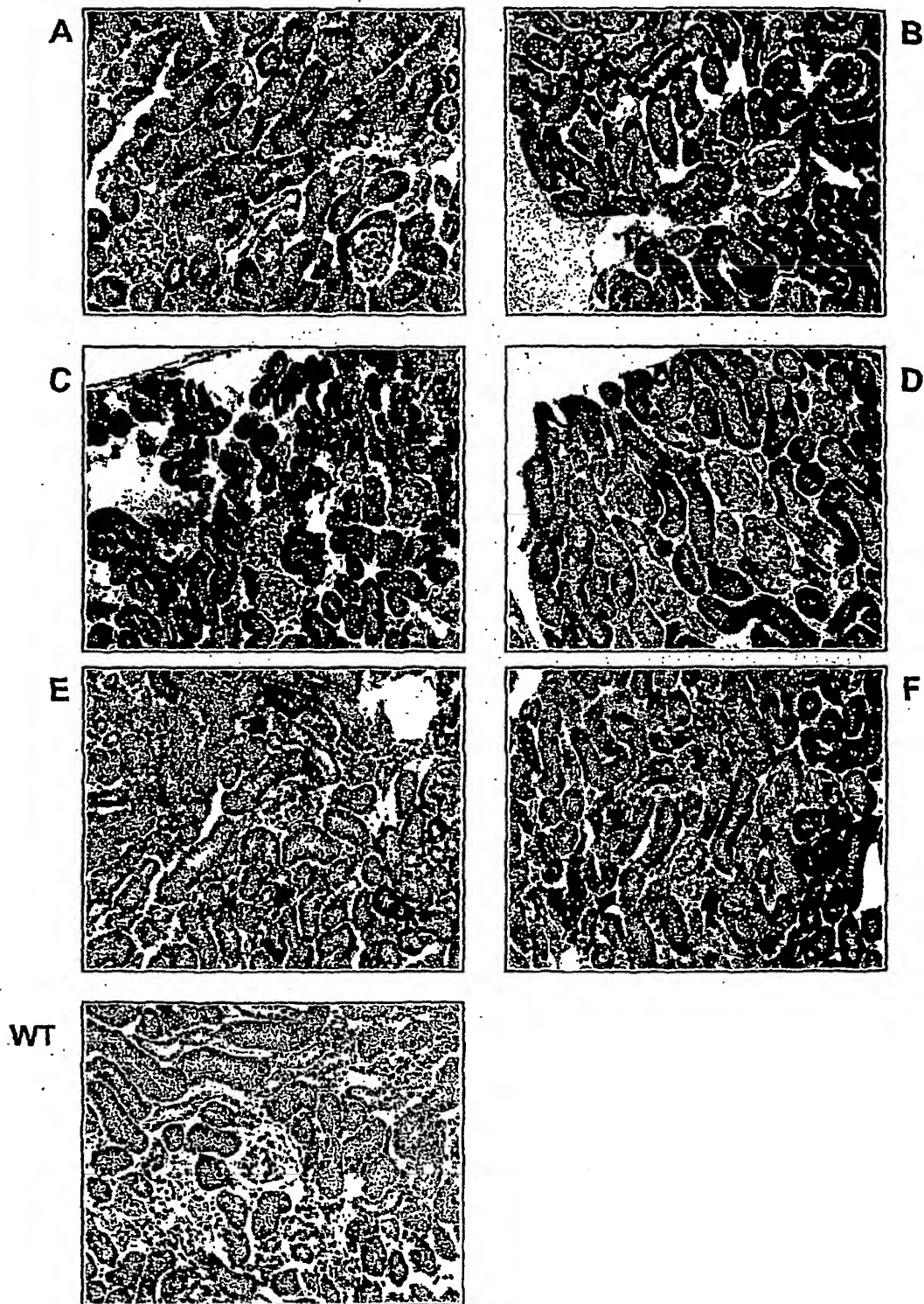


Fig. 18

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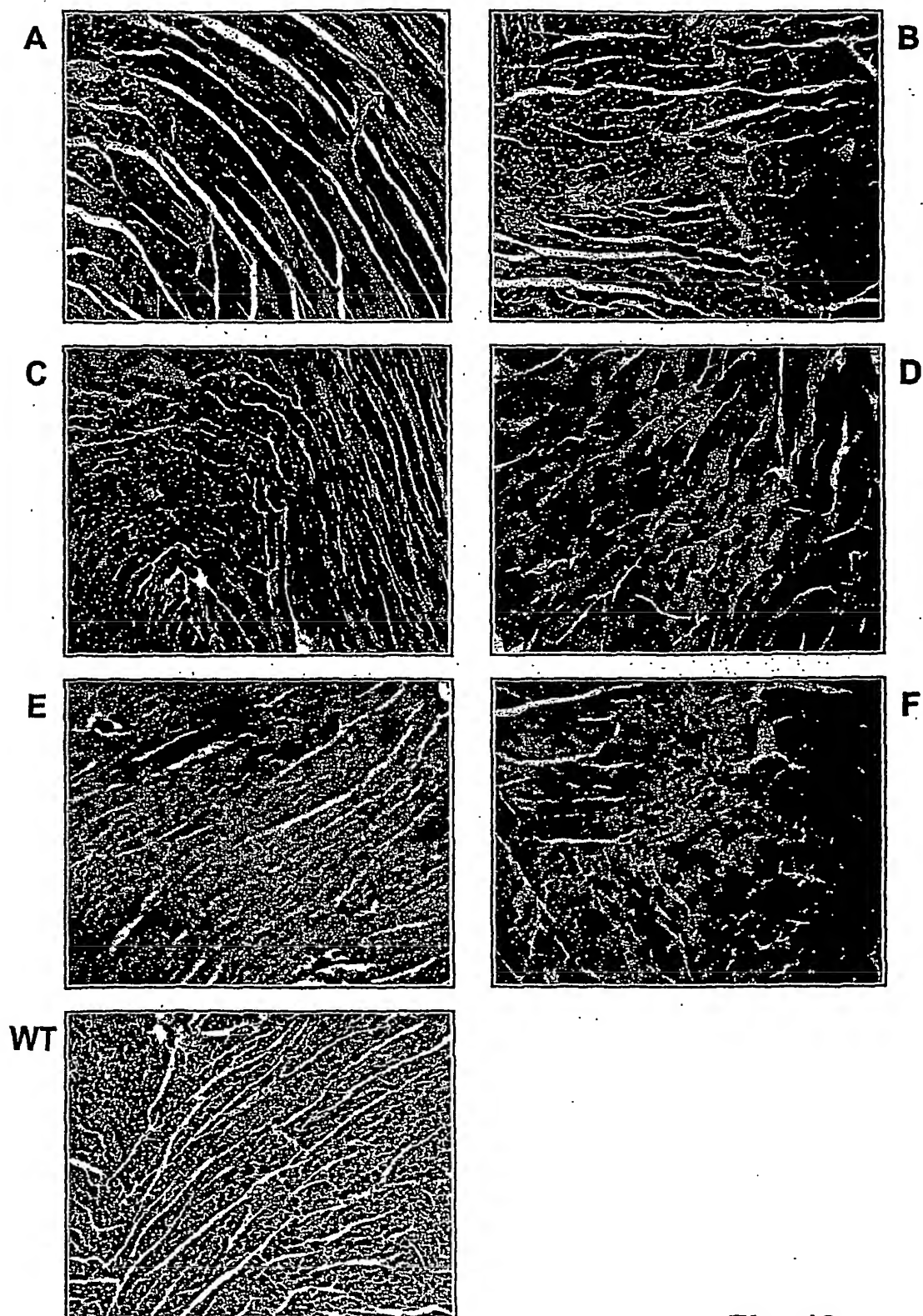


Fig. 19

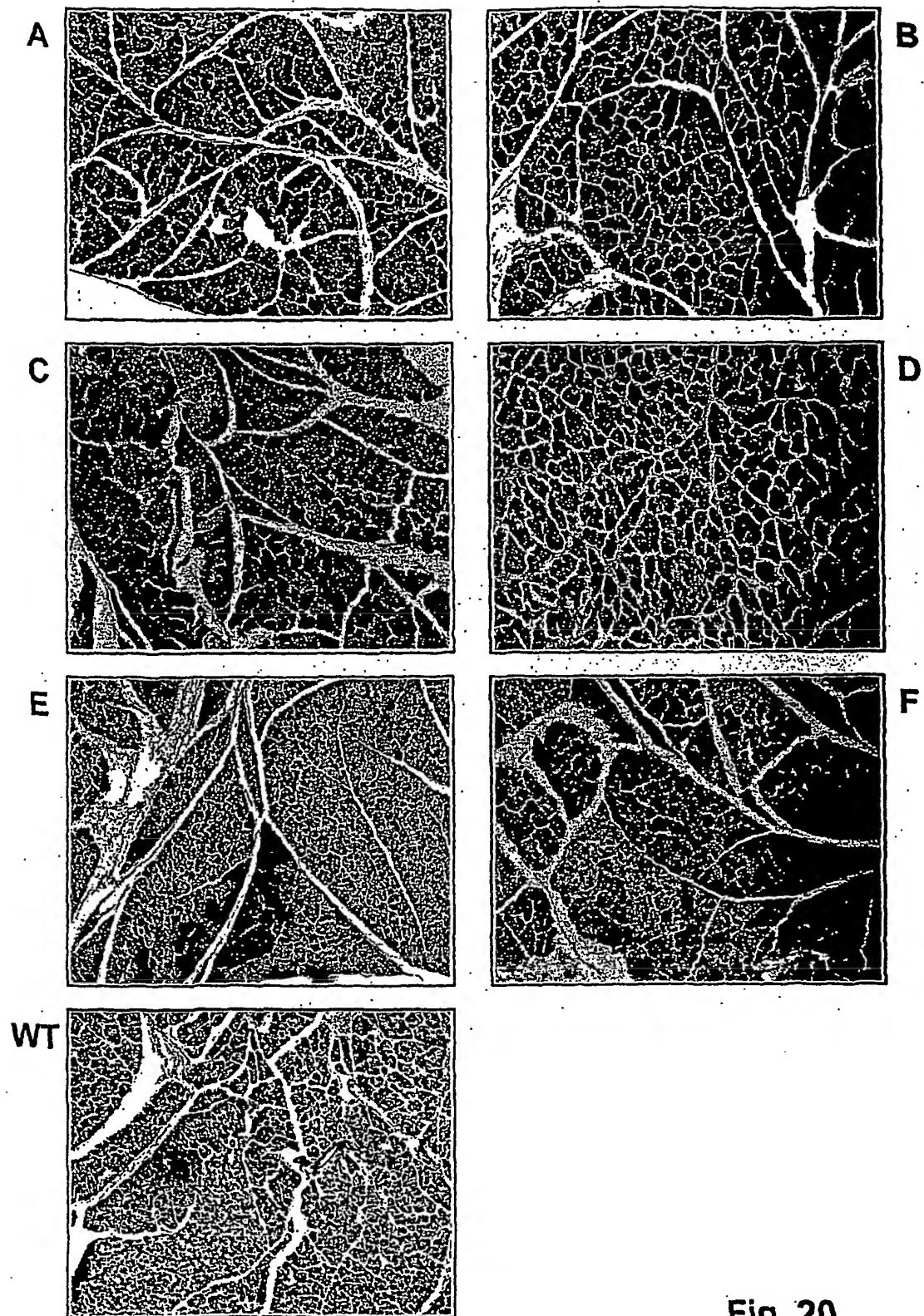


Fig. 20

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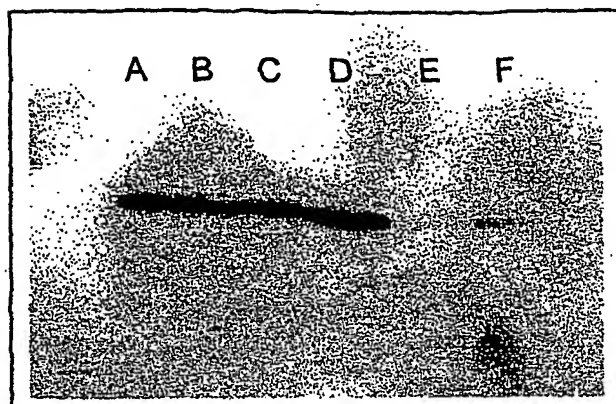


Fig. 21

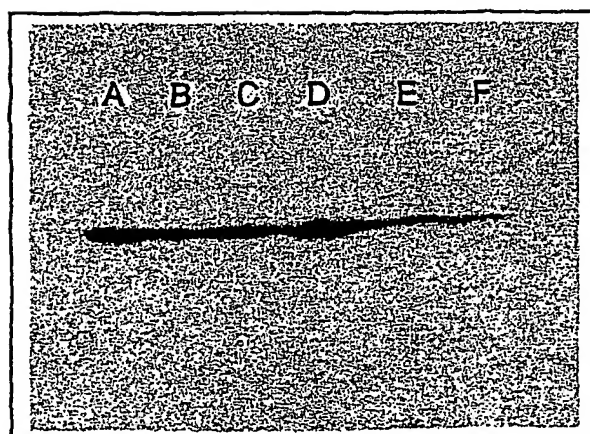


Fig. 22

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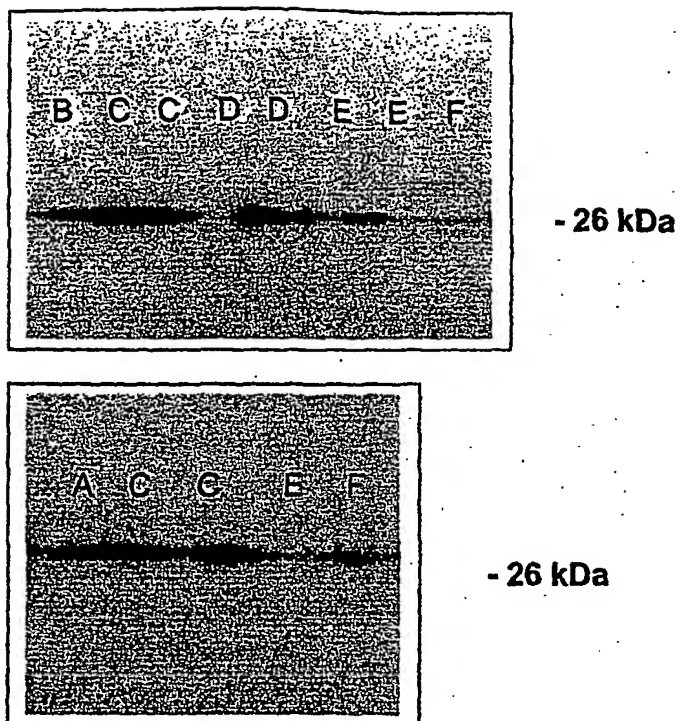


Fig. 23

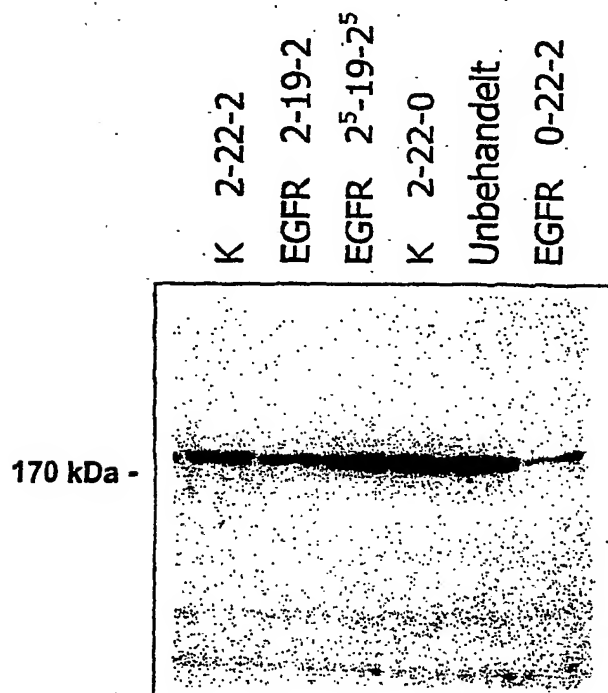


Fig. 24

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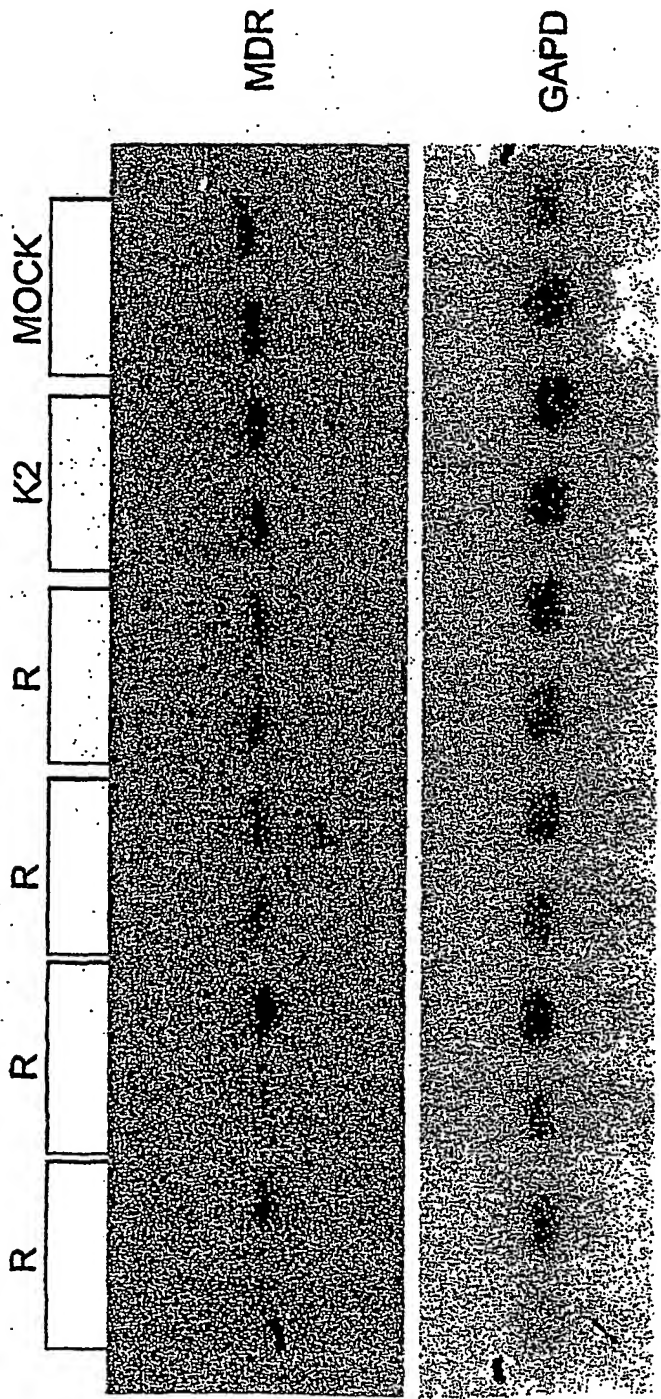


Fig. 25a

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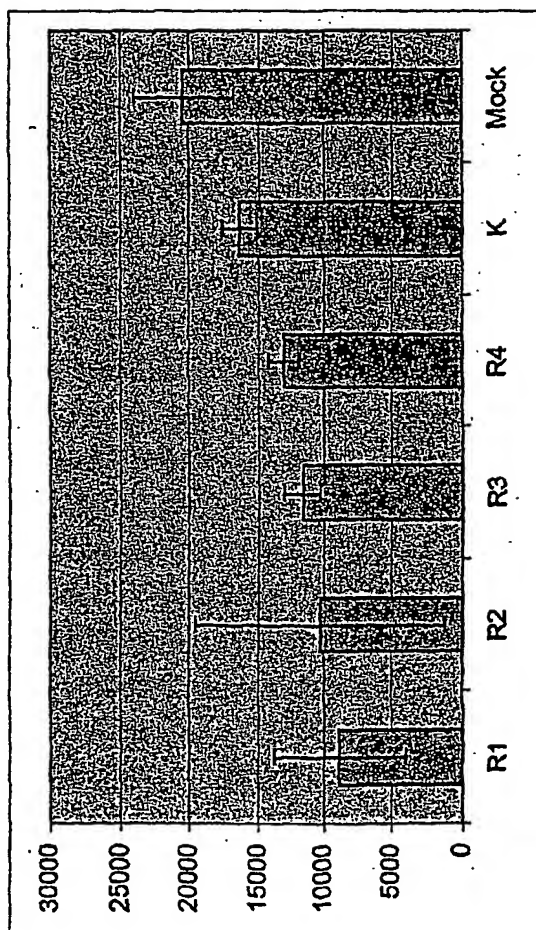


Fig. 25b

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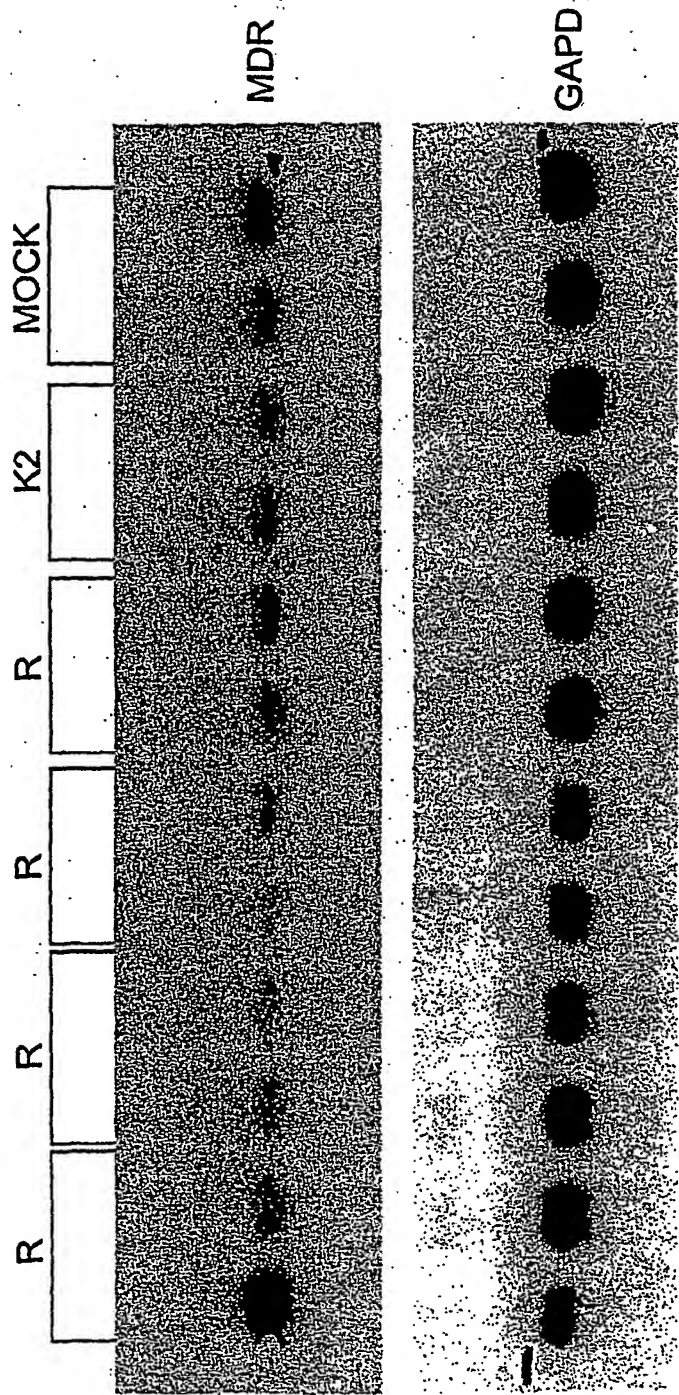


Fig. 26a

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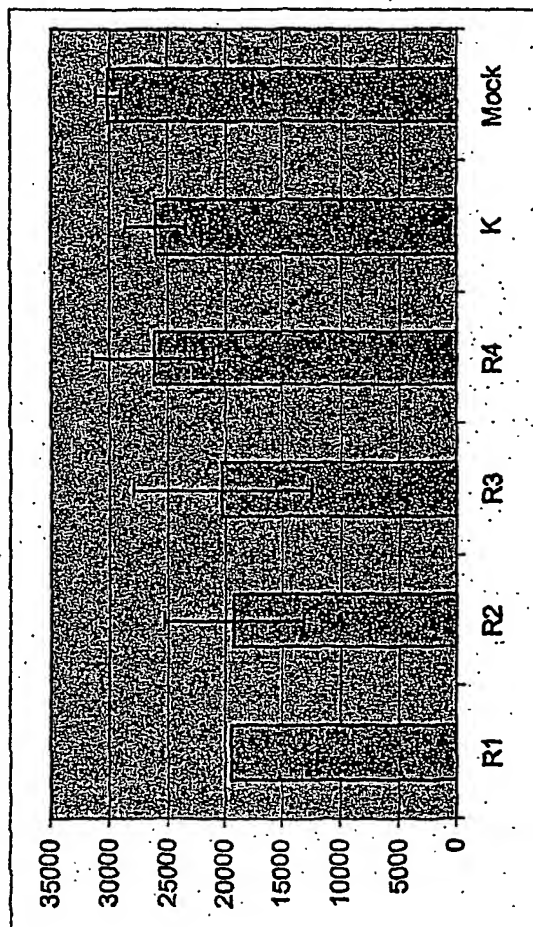


Fig. 26b

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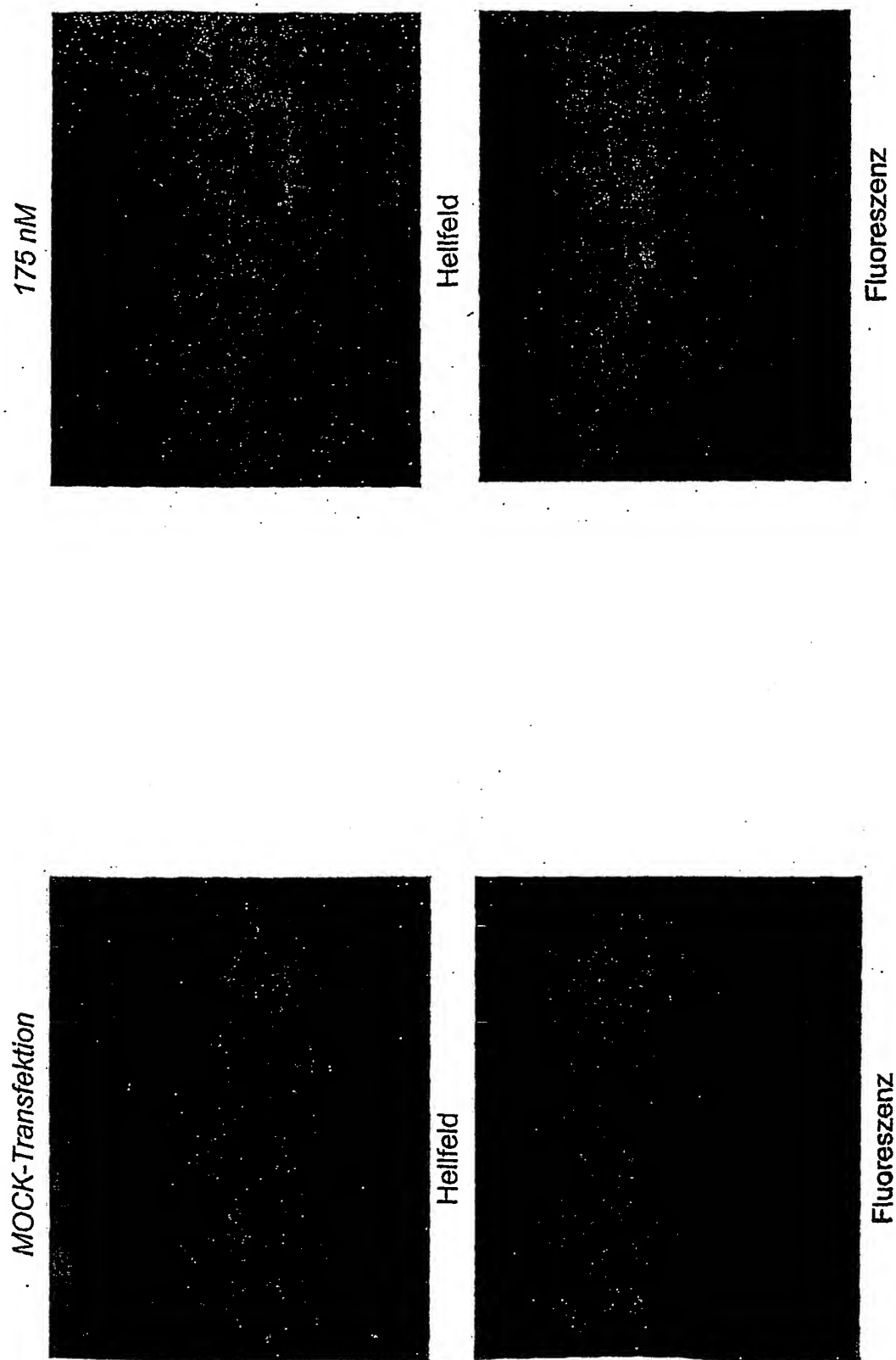
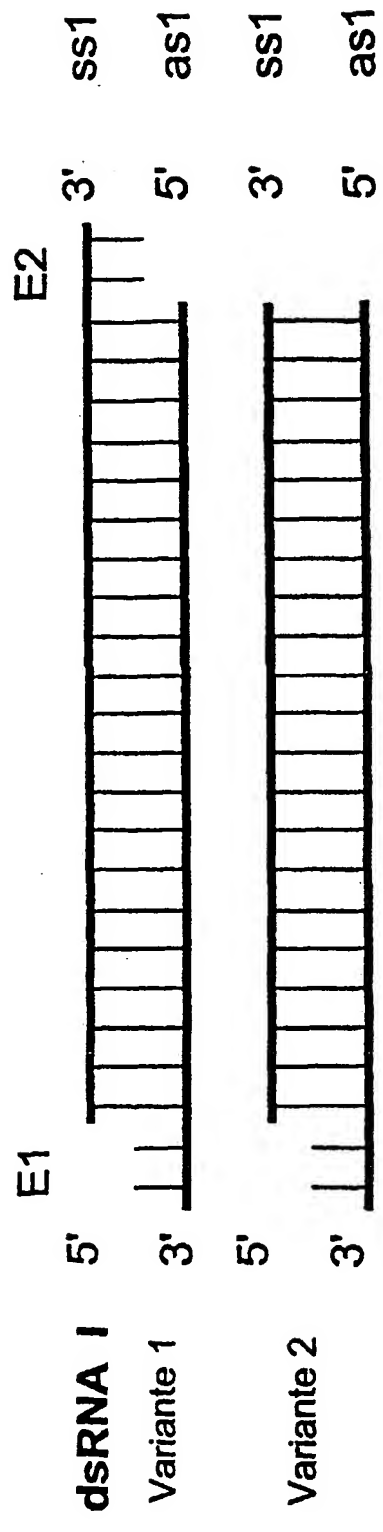


Fig. 27



(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro



(43) Internationales Veröffentlichungsdatum
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(10) Internationale Veröffentlichungsnummer
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101 55 280.7 26. Oktober 2001 (26.10.2001) DE
101 58 411.3 29. November 2001 (29.11.2001) DE
101 60 151.4 7. Dezember 2001 (07.12.2001) DE

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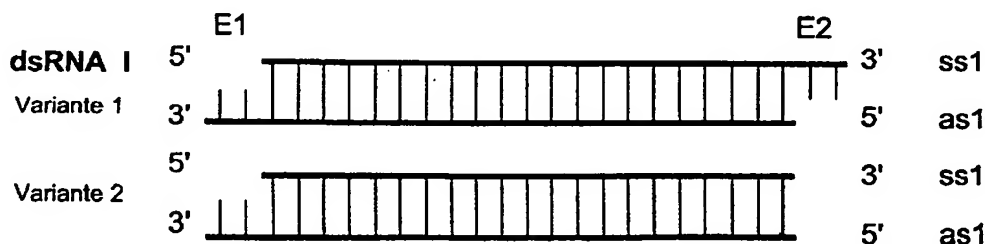
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US, UZ, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten (regional): ARIPO-Patent (GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), europäisches Patent (AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR),

[Fortsetzung auf der nächsten Seite]

(54) Title: METHOD FOR INHIBITING THE EXPRESSION OF A TARGET GENE

(54) Bezeichnung: VERFAHREN ZUR HEMMUNG DER EXPRESSION EINES ZIELGENS



(57) Abstract: The invention relates to a method for inhibiting the expression of a target gene in a cell, comprising the following steps: introduction of an amount of at least one dual-stranded ribonucleic acid (dsRNA I) which is sufficient to inhibit the expression of the target gene. The dsRNA I has a dual-stranded structure formed by a maximum of 49 successive nucleotide pairs. One strand (as1) or at least one section of the one strand (as1) of the dual-stranded structure is complementary to the sense strand of the target gene. The dsRNA has an overhang on the end (E1) of dsRNA I formed by 1 - 4 nucleotides.

(57) Zusammenfassung: Die Erfindung betrifft ein Verfahren zur Hemmung der Expression eines Zielgens in einer Zelle umfassend die folgenden Schritte: Einführen mindestens einer doppelsträngigen Ribonukleinsäure (dsRNA I) in einer zur Hemmung der Expression des Zielgens ausreichenden Menge, wobei die dsRNA I eine doppelsträngige aus höchstens 49 aufeinanderfolgenden Nukleotidpaaren gebildete Struktur aufweist, und wobei ein Strang (as1) oder zumindest ein Abschnitt des einen Strangs (as1) der doppelsträngigen Struktur komplementär zum Sinn-Strang des Zielgens ist, und wobei die dsRNA am einen Ende (E1) der dsRNA I einen aus 1 bis 4 Nukleotiden gebildeten Überhang aufweist.

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OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Veröffentlicht:

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(88) Veröffentlichungsdatum des internationalen

Recherchenberichts:

17. Juli 2003

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International Application No

PCT/EP 02/00152

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/11 A61K31/713 C12N15/88 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 44895 A (KREUTZER ROLAND ;LIMMER STEPHAN (DE)) 3 August 2000 (2000-08-03) the whole document ---	1-240
Y	WO 98 05770 A (ROTHBARTH KARSTEN ;JOSWIG GABY (DE); WERNER DIETER (DE); SCHUBERT) 12 February 1998 (1998-02-12) the whole document ---	1-240
Y	WO 99 32619 A (CARNEGIE INST OF WASHINGTON ;MONTGOMERY MARY K (US); FIRE ANDREW ()) 1 July 1999 (1999-07-01) the whole document ---	1-240
Y	WO 00 44914 A (FARRELL MICHAEL J ;LI YIN XIONG (US); KIRBY MARGARET L (US); MEDIC) 3 August 2000 (2000-08-03) the whole document ---	1-240
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Date of the actual completion of the international search

7 January 2003

Date of mailing of the international search report

27/01/2003

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Authorized officer

Armandola, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/00152

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZAMORE PHILLIP D ET AL: "RNAi: Double-stranded RNA directs the ATP-dependent cleavage of mRNA at 21 to 23 nucleotide intervals" CELL, CELL PRESS, CAMBRIDGE, NA, US, vol. 101, no. 1, 31 March 2000 (2000-03-31), pages 25-33, XP002208683 ISSN: 0092-8674 the whole document	1-240
Y	BASS BRENDA L: "Double-stranded RNA as a template for gene silencing" CELL, CELL PRESS, CAMBRIDGE, NA, US, vol. 101, no. 3, 28 April 2000 (2000-04-28), pages 235-238, XP002194756 ISSN: 0092-8674 figure 1	1-240
Y	UHLMANN E ET AL: "ANTISENSE OLIGONUCLEOTIDES: A NEW THERAPEUTIC PRINCIPLE" CHEMICAL REVIEWS, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 90, no. 4, 1 June 1990 (1990-06-01), pages 543-584, XP000141412 ISSN: 0009-2665 the whole document	20-30, 60-70, 99-109, 140-150, 180-190, 219-229
Y	PARRISH S., FLEENOR J., ET AL.: "Functional Anatomy of a dsRNA trigger: differential requirement for the two trigger strands in RNA interference." MOL. CELL, vol. 6, November 2000 (2000-11), pages 1077-187, XP002226361 the whole document	1-240
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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	ELBASHIR SAYDA M ET AL: "RNA interference is mediated by 21- and 22-nucleotide RNAs" GENES AND DEVELOPMENT, COLD SPRING HARBOR LABORATORY PRESS, NEW YORK, US, vol. 15, no. 2, 15 January 2001 (2001-01-15), pages 188-200, XP002204651 ISSN: 0890-9369 the whole document	1-240
A	WO 94 01550 A (AGRAWAL SUDHIR ;HYBRIDON INC (US); TANG JIN YAN (US)) 20 January 1994 (1994-01-20)	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/00152

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 C12N15/11 A61K31/713 C12N15/88 A61P35/00

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EPO-Internal, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data, SEQUENCE SEARCH

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 00 44895 A (KREUTZER ROLAND ;LIMMER STEPHAN (DE)) 3. August 2000 (2000-08-03) das ganze Dokument	1-240
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Y	WO 99 32619 A (CARNEGIE INST OF WASHINGTON ;MONTGOMERY MARY K (US); FIRE ANDREW ()) 1. Juli 1999 (1999-07-01) das ganze Dokument	1-240
Y	WO 00 44914 A (FARRELL MICHAEL J ;LI YIN XIONG (US); KIRBY MARGARET L (US); MEDIC) 3. August 2000 (2000-08-03) das ganze Dokument	1-240

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Armandola, E

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
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